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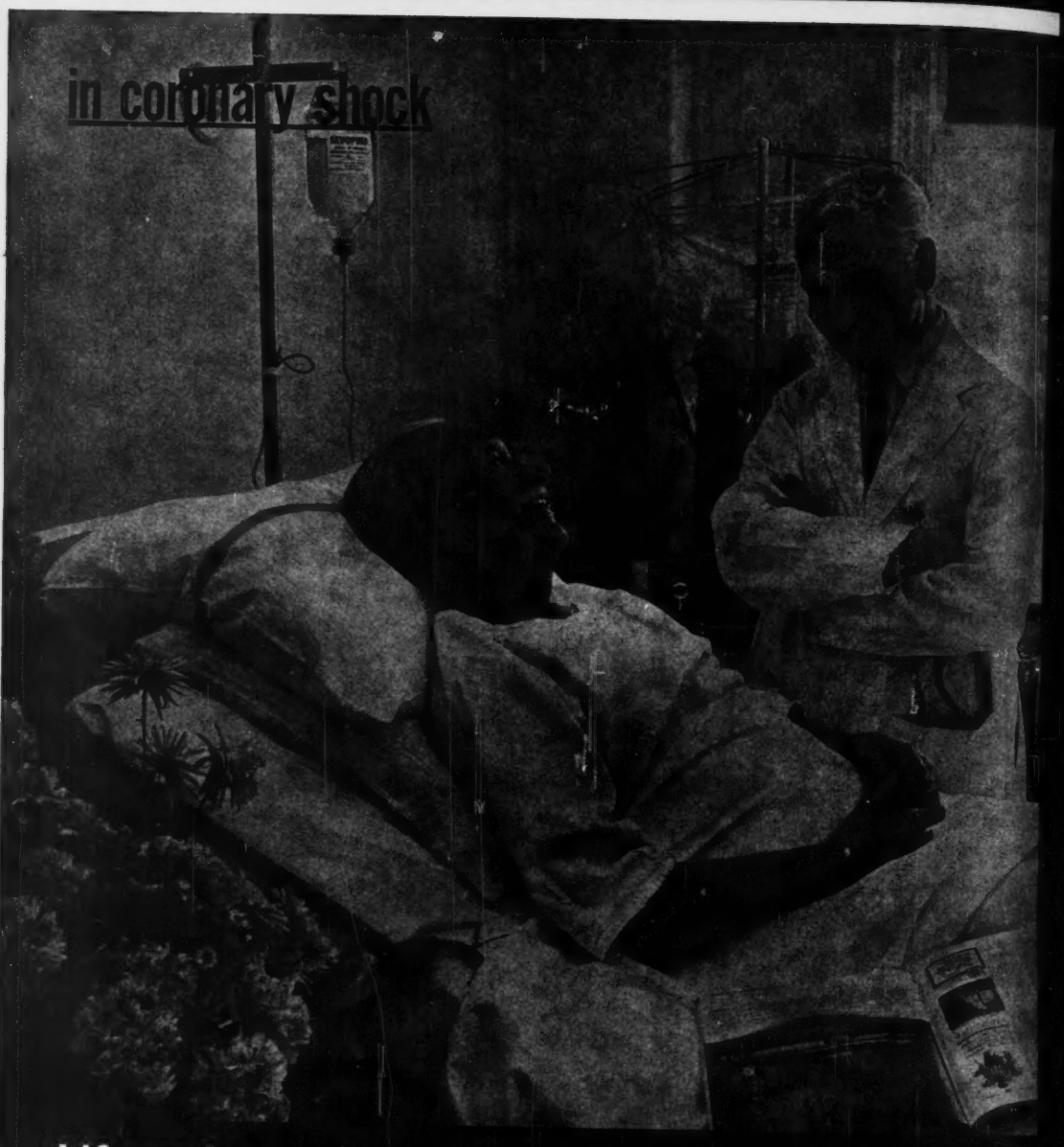

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1. Miller, A. J., and Moser, E. A.: J.A.M.A. 169:2087, April 25, 1959.

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Editorial

Genetics and the Nature of Essential Hypertension

By VICTOR A. MCKUSICK, M.D.

NO ONE now seems to doubt that essential hypertension "runs in families" and that this familial aggregation is in large part genetically determined. Evidence on the heritability of hypertension[1] has been provided by family studies, comparisons in monozygotic and dizygotic twins, comparisons of different racial groups, and the demonstration of the genetic determination of essential hypertension in certain strains of rabbits.

The role of heredity in hypertension is of more than mere academic interest. The elucidation of genetic factors has a bearing on the answer to the questions: What is essential hypertension? Is essential hypertension a pathogenetic and etiologic entity? On the answer to these questions might depend how one will choose to approach the study of basic mechanisms in this common disorder.

Prior to the work of Pickering and his colleagues,[2] most viewed essential hypertension as a distinct disease entity—a pathologic characteristic for which persons could be classed "plus" or "minus," affected or unaffected. Arbitrarily defining what elevations of blood pressure constitute hypertension, several workers such as Platt[3] suggested that essential hypertension is a hereditary, Mendelian dominant characteristic.

The work of Pickering and his associates demonstrated that blood pressure describes a continuous frequency distribution which is unimodal, that no separation into a hypertensive class and a normotensive class is evident. Studies by Bøe,[4] in Bergen, Norway, by Comstock,[5] in Georgia, and by others corroborated the continuous distribution (fig. 1). Although the curves from all studies demonstrate a positive skew and leave open the possibility that two distinct populations are represented (fig. 2*A*), the conclusion of Pickering and his colleagues has been that blood pressure level is a multifactorial trait, comparable to stature, intelligence, ocular refraction, and many other traits. The corollary is that one does not inherit essential hypertension; rather one tends to inherit a particular level of blood pressure. "Essential hypertension is not a disease," is a dramatic way to put it. The persons labeled as suffering from essential hypertension are considered to be those whose blood pressure falls in the upper end of a "bell-shaped" continuous distribution. The genetic determination of hypertension is thought to be polygenic in nature and not susceptible to interpretation in terms of a simple Mendelian dominant or recessive. Presumably the multiple genetic factors operate, each through a different mechanism, to influence blood pressure. Although one could hope eventually to learn to define many or all of such multiple genetic mechanisms, the prospects are less bright than would be the case if genetic analysis suggested unifactorial inheritance and therefore a unitary biochemical defect.

From the Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

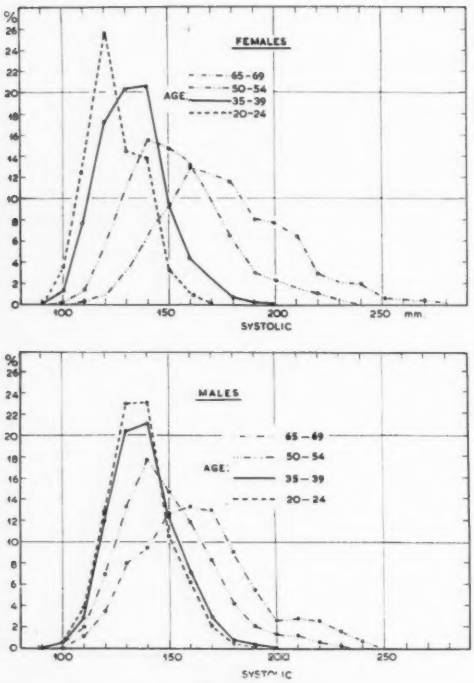
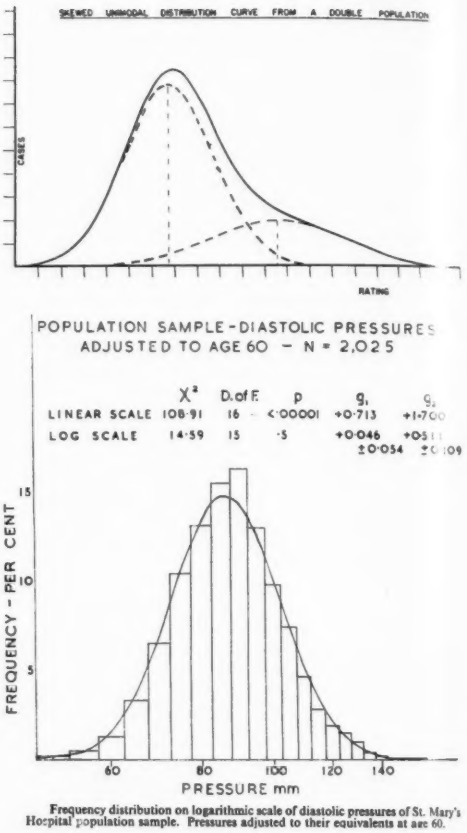


Figure 1

The curves illustrate the "continuous," unimodal frequency distributions, with positive skew, discovered in many population studies of hypertension. The population represented here consisted of almost 68,000 persons resident in Bergen, Norway. (From Bφe, J., Humerfelt, S., and Wedervang, F.: Acta med. scandinav. **157** *(Suppl. 321), 1957.)*



Frequency distribution on logarithmic scale of diastolic pressures of St. Mary's Hospital population sample. Pressures adjusted to their equivalents at age 60.

Figure 2

The positive skew of the frequency distributions illustrated in figure 1 has at least two possible explanations (which are not mutually exclusive): The skew may indicate that two populations are represented, as is schematized in figure 2A (upper) *(courtesy of Dr. E. A. Murphy). Or it may be that a linear calibration of the blood pressure scale is not biologically the proper one. For example, a logarithmic blood pressure scale giving a log-normal plot[16] of the frequency distribution may be more accurate. Indeed, as seen in figure 2B* (lower), *the skew in blood pressure data disappears when such a plot is used. (From J. A. F. Roberts[15]).*

Against this background the report of Platt[6] and that of Morrison and Morris[7] are of great interest. Both come to the conclusion that indeed two populations with reference to blood pressure are demonstrable and that there is bimodality consistent with the existence of a single major genetic factor in the etiology of essential hypertension.

Sir Robert Platt of Manchester reanalyzed the data of Pickering and his colleagues[8] and of Søbye.[9] The blood pressure of hypertensive probands and their sibs aged 45 to 60 years was used because (1) one could expect thus to exclude a certain number of cases of secondary hypertension which in Platt's experience is more frequent than essential hypertension under the age of 40 years, and (2) the necessity for age correction is avoided. A bimodality was shown for systolic pressures and was suggestive for diastolic pressures. As a hypothetical example Platt pointed out that if hypertension affects about 19 per cent of middle-aged persons (figure

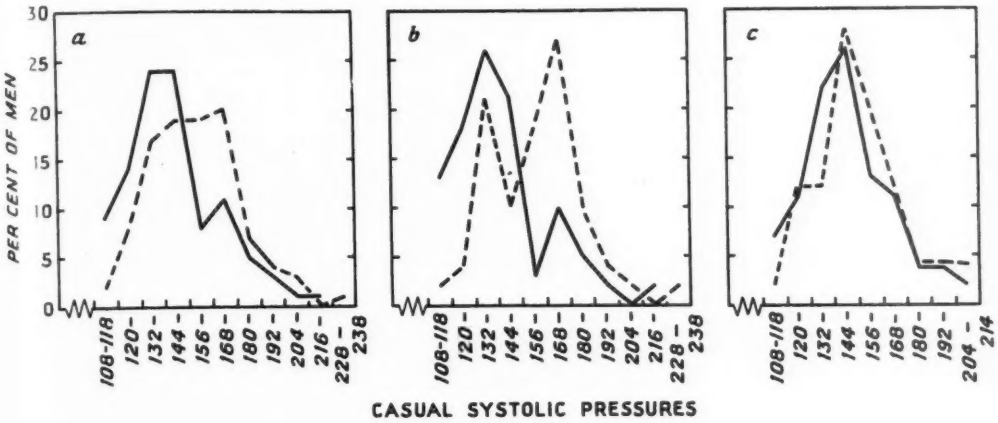


Figure 3A

Distributions of casual systolic blood pressures in bus drivers aged 45 to 60 years: (a) all drivers (186 men); (b) drivers with one or both parents dead in middle age (90 men) (middle age, 40 to 64 years); (c) drivers with both parents living to old age (96 men) (old age, 65 years or over).

chosen in part for convenience) and that if hypertension is a simple dominant trait then the incidence of the three genotypes becomes as follows:

q^2 = .81 ("normals")
2 pq = .18 (hypertensive subjects, heterozygous for dominant gene)
p^2 = .01 (hypertensive subjects, homozygous for dominant gene)

And among the sibs of a hypertensive proband the proportion of hypertensive sibs is 0.58:

$$1 - \frac{pq^2(1-p/4)}{1-q^2} = 0.58$$

The figure of 58 per cent is essentially the frequency among sibs in the data analyzed by Platt.

What clinical form hypertension would take in the person homozygous for this postulated dominant gene is interesting to speculate. Are persons with accelerated phase of essential hypertension, i.e., "malignant hypertension," recruited from this group?

The old uncertainty about what level of blood pressure is hypertension might, Platt suggested, be resolved to some extent by those curves showing bimodality. If the antimode is taken as the threshold for hypertension in the 45 to 60 year group, then a blood pressure of 160/95 mm. is the approximate point above which hypertension can be said to be present in this age group.

As in Morris' studies of coronary artery disease, data from the drivers and conductors of London buses were used by Morrison and Morris. The data of blood pressure had been collected previously without this particular analysis in mind. Although the curve for blood pressure in all cases was essentially continuous, that for those men in whom one or both parents had died in middle age was found to be bimodal (fig. 3*A*). This suggested the existence of two groups, one of which inherited the "dominant" gene and one of which did not. A reciprocal analysis involved the plotting of age of death in the fathers of hypertensive drivers. Here a distinct bimodality was demonstrated (fig. 3*B*), suggesting that part of the hypertensive drivers inherited the "dominant" gene from the father and part inherited it from the mother. The authors quoted a paper of Harris and Smith,[10] who, in discussing a different problem, analyzed the considerations determining whether bimodality is evident in a distribution curve which in fact contains

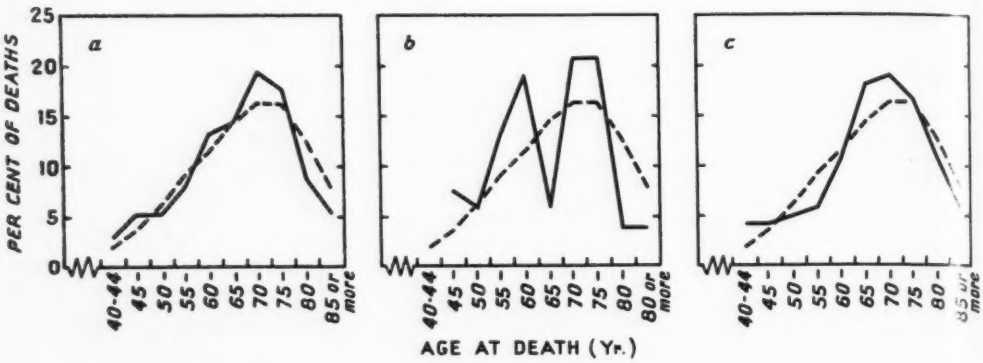


Figure 3B

Distribution of ages at death (from all causes) in fathers of bus drivers aged 45 to 60 years. The interrupted line represents the distribution of ages at death of all men in England and Wales: (a) fathers of all drivers (174 deaths); (b) fathers of "hypertensive" (B.P. 160/95 mm. Hg or over) drivers (53 deaths); (c) fathers of "normotensive" drivers (121 deaths). (From Morrison, S. L., and Morris, J. N.: Lancet **2**: *864, 1959.)*

two populations: relative sizes of the populations, degree of separation of the modes, the standard deviations in the populations, etc.

If a single major genetic factor in essential hypertension is assumed, a unitary defect in a biochemical mechanism becomes plausible and seems worth seeking. (For example, Mendlowitz' suggestion[11] of a defect in the enzyme O-methyl transferase would be consistent with the genetic information.) It is possible to imagine that unitary biochemical defect, once found, could become the basis for preclinical diagnosis, definitive therapy, and prophylaxis.

As both Platt, and Morrison and Morris, have indicated, much needed are more longitudinal data to answer the question: Are there two types of persons, one in whom blood pressure rises with advancing years and one in whom blood pressure rises very little or not at all? Although mean pressure rises with age, it may be that only the average is raised by those individuals who for genetic reasons show a rise with age. The increase in variance of the blood pressure of groups with increasing age (fig. 4) could be so explained. Robinson and Brucer[13] presented data consistent with the existence of two populations (fig. 5). Cruz-Coke,[14] of Chile, from a study of civil servants spanning 12 years, found that persons hypertensive at the end of the period had had diastolic pressures in the normal range (although in the upper part of that range) at the beginning of the period.

Bimodality of blood pressure increment should be sought in longitudinal data. A study performed in a population as homogeneous as possible in racial background and environmental circumstances and designed to reduce extraneous sources of variability to a minimum might be ideal. Longitudinal studies among first-degree relatives of hypertensive patients would be expected to be particularly revealing because the two postulated populations should be more nearly equal in size.

The rebuttal[17–20] to Platt and Morrison and Morris has taken the following arguments:

1. Cruz-Coke[19] indicated that he would prefer the demonstration of bimodality in *diastolic* pressure, which he suggested is a better indicator of essential hypertension, being less affected by factors such as stroke volume and aortic rigidity.

2. Keen and Rose[18] showed that bimodality among the offspring of parents dying in

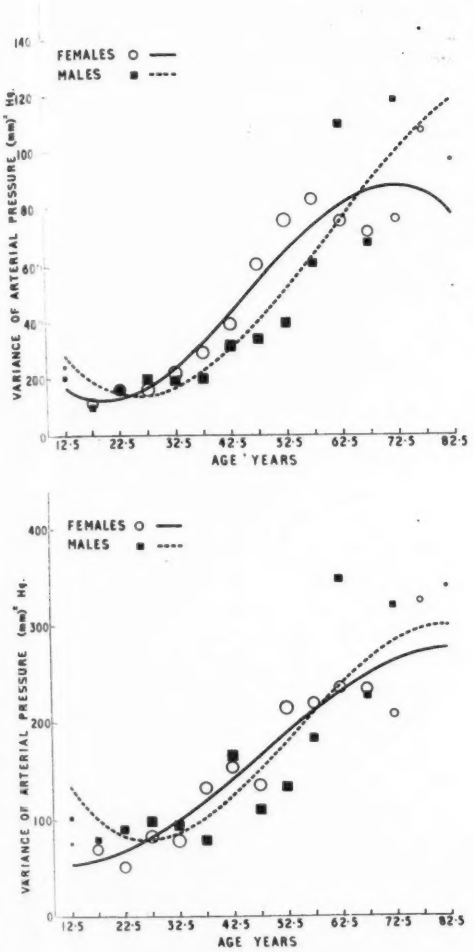


Figure 4

Relationship between age and variability in systolic (upper) *and diastolic* (lower) *blood pressures. The areas of the circles (females) and of the squares (males) are proportional to the number of subjects (From Hamilton, M., Pickering, G. W., Roberts, J. A. F., and Sowry, G. S. C.:* Clin. Sc. 13: *, 1954.)*

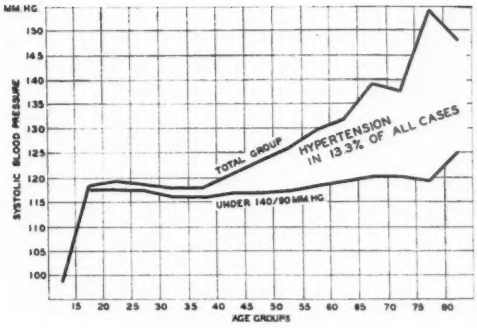


Figure 5

Average blood pressure against age in 7,478 men. The upper curve indicates the rise in average pressure with age in the total group. However, when those cases of blood pressure over 140/90 mm. Hg (13.3 per cent of all cases) are removed, there is in the remaining group little change in pressure with age. (From Robinson, S. C., and Brucer, M.: Arch. Int. Med. **64:** *409, 1939.)*

middle age is not inconsistent with the polygene hypothesis: The offspring of those dying of hypertension should demonstrate blood pressures distributed around a high mean and the offspring of those dying of causes other than hypertension should demonstrate blood pressures distributed around a lower mean approaching the mean of the general population.

3. In the follow-up data on blood pressure[21] collected in Wales by Dr. W. E. Miall, no differences in rate of rise of blood pressure in the relatives of "hypertensives" as compared with relatives of "normotensives" could be demonstrated by Oldham, Pickering, Roberts, and Sowry.[20]

4. Pickering's group and Søbye began the studies which yielded the data analyzed by Platt with the bias that hypertension indeed is genetically unifactorial and that subjects can be classed without difficulty as affected or unaffected. Possibly there was a tendency unconsciously to shun the value of 150/90 mm. Hg. The medical mind may abhor uncertainty. Although the data of Morrison and Morris were collected without the analysis in mind the same psychologic factors may have been operative. The data of Miall and Oldham[21, 22] have the virtue that all pressures were taken by a single observer (Dr. W. E. Miall, a former student of Pickering at St. Mary's Hospital). At the time of their study the alternative multifactorial hypothesis had been advanced.

The other arguments of the rebuttal are restatements of points made earlier:

1. That the polygenic theory makes better physiologic sense in light of the multiple factors known to influence level of blood pressure.

2. That elevated blood pressure is *per se* not a clinical or pathologic entity but rather the complications of hypertension are responsible for clinical and anatomic abnormalities; and others.

That the correlation between the blood pressure of probands and first-degree relatives is the same (about 0.2) at all levels of pressure in the proband[23] is possibly in keeping more with the polygenic hypothesis. So is the racial difference between Negroes and whites living under apparently similar circumstances in southern United States.[5] However, with a considerable environmental factor in blood pressure, intrafamilial similarities and interracial differences in environment might be invoked to account for the data on a unifactorial genetic basis.

The difficulties in interpreting the genetics of hypertension—and in the opinion of one school, the ease of misinterpreting polygenic inheritance as unifactorial dominant inheritance—is illustrated nicely by the example of "distal hyperextensibility of the thumbs." When measured as the angle of maximal extension of the terminal phalanx of the thumbs the character displays a unimodal continuous distribution. Yet using an arbitrarily designated angle of extension as the point of separation between "affected" and "unaffected," Glass[24] could demonstrate good agreement of family data with a dominant hypothesis. Arguments based on calculations of supposed gene frequencies (see above) are suspect, since a fit to a single gene hypothesis can be attained by manipulation of data on a polygenic trait.

It can be concluded that the evidence is sufficiently susceptible to conflicting interpretation to warrant an open mind. Certainly, even the existence of evidence for polygenic inheritance does not preclude the desirability of searching for a unitary, genetically determined biochemical defect, the expression of which is modified by environmental and other genetic factors.

VICTOR A. MCKUSICK

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Heredity vs. Environment

We are all tattooed in our cradles with the beliefs of our tribe; the record may seem superficial, but it is indelible—OLIVER WENDELL HOLMES, M.D. *The Poet at the Breakfast Table,* 1872.

The George E. Brown Memorial Lecture

Circulatory Congestion and Heart Failure

By LUDWIG W. EICHNA, M.D.

IN ACCEPTING the honor, and the responsibility, of the George E. Brown Lectureship for 1959 I do so, not for myself, but for a fine group of stimulating colleagues. It is their work and their thinking that will constitute the substance of this lecture. This presentation will, therefore, have a personal and restricted focus, a desirable feature in that one area and one viewpoint is examined in depth, an undesirable feature in that many pertinent investigations by others are not given the attention that they certainly merit.

Man, almost alone, develops spontaneously the syndrome of congestive heart failure. Accordingly, the observations to be presented have all been derived from man. They will examine the interrelationships between the two major manifestations of the circulation in congestive heart failure, namely, circulatory congestion and reduced cardiac output. Three principal areas will be considered: (1) the nature of circulatory congestion and its significance as an index of heart failure, (2) the effect of the circulatory congestion itself on the function of the heart and on the function of one peripheral organ, the kidney, and (3) the relation of lowered cardiac output to circulatory congestion and to activity and survival.

From the Department of Medicine, New York University College of Medicine and the Third (New York University) Medical Division, Bellevue Hospital, New York, N. Y.

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Dr. Eichna's present address: State University of New York, Downstate Medical Center, Brooklyn, N.Y.

Circulatory Congestion as an Index of Heart Failure

A cardinal feature of congestive heart failure is the presence of circulatory congestion. This congestion involves the venous beds behind either the right side of the heart, the left side, or both. Venous congestion behind the right ventricle produces the characteristically distended veins, the enlarged liver, and the edema; congestion behind the left ventricle causes the dyspnea, orthopnea, and pulmonary rales. It is these manifestations of circulatory congestion that the clinician recognizes at the bedside; their cause he must infer. Clinicopathologic correlation long ago established that these congestive changes occur in patients with heart disease and, more recently, hemodynamic determinations have demonstrated that in such cardiac patients the output of the heart is decreased below normal.[1-7] As a consequence, the presence of circulatory congestion, regardless of the circumstances under which it appears, has come to be accepted as diagnostic of heart failure and specifically of failure of the myocardium to circulate adequate amounts of blood.

The first point to be examined is whether this traditional concept is correct.[8] Consider the situation that results from the administration of excessive intravenous infusions[9-13] to a patient with a normal heart, particularly if there is oliguria, as in lower nephron nephrosis. The normal heart is important to the argument. Blood volume is artificially increased, circulatory distention develops and with it appear the characteristic manifestations of circulatory congestion, already detailed. The clinical picture is similar to indeed indistinguishable from, congestive heart failure. But has the heart failed? It is difficult to understand how the heart by improv-

Table 1

Categories of Non-cardiac (Non-myocardial) Circulatory Congestion

I.	*Obstruction (cardiac)*—mitral stenosis, tricuspid stenosis, constrictive pericarditis, rapid tachycardias.
II.	*Excessive water and salt retention*—steroid medication, anuria (toxic), acute glomerulonephritis.
III.	*Hyperkinetic states*—anemia, beriberi, arteriovenous fistula.

ing any of its functions, including increasing the cardiac output, can relieve the circulatory congestion. This situation illustrates the hemodynamic disturbances here designated noncardiac circulatory congestion. Its clinical manifestations are essentially similar to those of congestive heart failure; its cause, however, is not failure of the heart muscle.

A series of correlated hemodynamic observations by Farber, Berger, Rader, Smith, and Albert[14] indicated that both systemic and pulmonic vascular congestion may rise on a noncardiac basis to produce a clinical syndrome that closely simulates congestive heart failure. The data suggested 3 categories (table 1) of such noncardiac circulatory congestion, and the patients in each category have been traditionally considered to have congestive heart failure.

Category I is characterized by mechanical obstruction to flow in or about the heart, and includes patients with constrictive pericarditis, tricuspid stenosis, and most typically the severe, "pinch-cock" mitral stenosis without significant myocardial involvement, as indicated by the absence of right ventricular failure and by a normal-sized or slightly enlarged heart. The roentgenographic silhouette does not always give a true impression of the nature of cardiac enlargement. For example, in a patient (T. R.) with severe mitral stenosis the huge cardiac silhouette extending from chest wall to chest wall, was due to a giant left atrium. The ventricles, the propelling component of the heart, were of normal size and weighed 300 Gm.

Category II is characterized by the accumulation of excessive amounts of water and salt in patients with normal hearts and includes the edematous states associated with the following conditions: the administration of large amounts of salt-retaining steroids,[15] anuria, or oliguria as in lower nephron nephrosis,[16, 17] and acute diffuse glomerulonephritis.[18, 19] Albert and Smith[15] observed that noncardiac subjects who became edematous when receiving large doses of corticotropin (ACTH) or salt-retaining steroids developed not only symptoms of dyspnea and orthopnea but also enlarged cardiac silhouettes and evidences of pulmonary congestion. The associated hemodynamic changes were increased vascular and intracardiac pressures of a degree similar to congestive heart failure, but cardiac output remained normal. Following cessation of medication hemodynamic alterations and heart size returned to normal. The edema and circulatory congestion of acute nephritis is also associated with cardiac enlargement but the heart again returns quickly to normal size following diuresis (fig. 1*A*, *A'*).

Category III is characterized by circulatory congestion in the hyperkinetic circulatory states, the so-called "high output heart failure," and includes the edematous states occurring in beriberi, arteriovenous fistula, and severe anemia, again in patients with normal hearts.[20–24] The cardiac enlargement and circulatory congestion in these patients subside with specific but noncardiac medication and the heart returns to normal size (fig. 1*B*, *B'* and 1*C*, *C'*).

The characteristically normal heart size after recovery from circulatory congestion is a significant differentiating feature that separates these noncardiac patients from typical congestive heart failure, in which the heart remains enlarged even after recovery of compensation.

If these 3 types of circulatory congestion are truly noncardiac, that is, nonmyocardial in origin, they should differ from typical con-

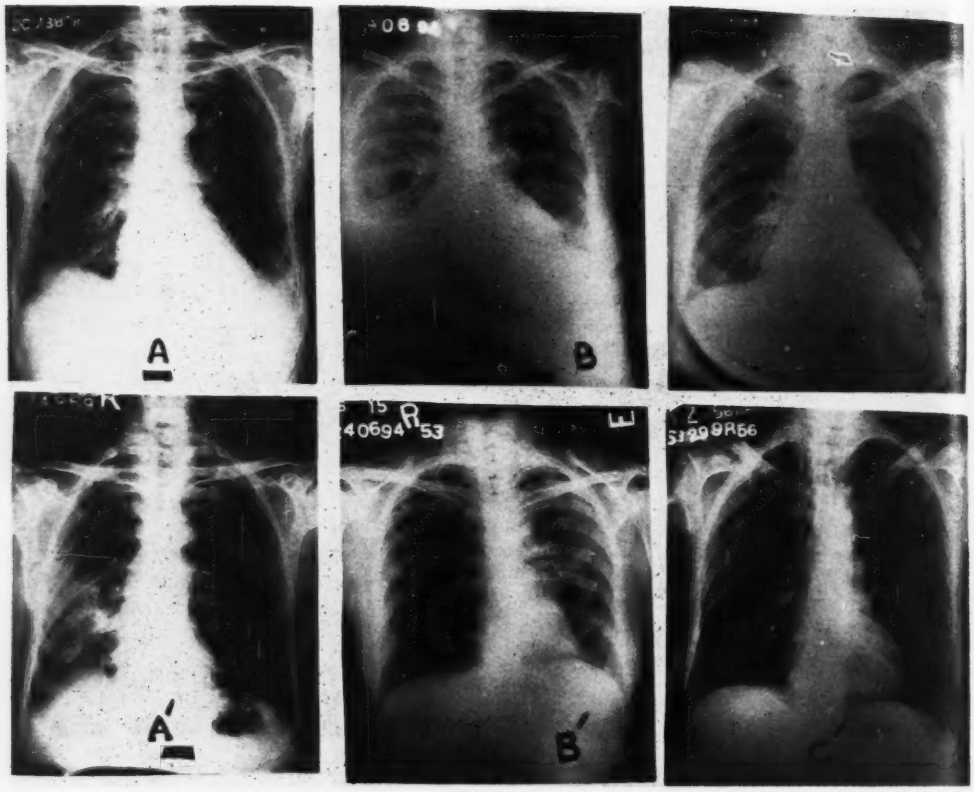

Figure 1

Heart size in circulatory congestion due to excess water and salt retention (A) *and hyperkinetic states* (B, C). *For each vertical panel the upper x-ray was taken during circulatory congestion and the corresponding lower x-ray after recovery from congestion following noncardiac medication.* A,A', *M.K., male, 70 years, acute glomerulonephritis.* B.B.', *M.M., female, 38 years, beriberi.* C,C', *W.S., male, 48 years, severe anemia.*

gestive heart failure, occurring in patients with heart disease, in significant hemodynamic functions. Accordingly, differences were sought and indeed were observed,[14] in 3 hemodynamic parameters: the dynamics of cardiac function; the circulation and function of peripheral organs—the kidney was chosen for study because of its key role in edema formation; and the hemodynamic and clinical response to specific medication.

Consider first the parameter of circulation and cardiac function. With respect to intracardiac pressures (fig. 2), the pressures in the pulmonary artery, right ventricle, and right atrium were elevated above normal in patients in each of the 3 categories of noncardiac circulatory congestion, and these elevations were generally comparable to the values in congestive heart failure. The normal right atrial pressure in "pinch-cock" mitral stenosis is expectedly not elevated, since the right ventricle does not fail in this situation and right-sided congestion is absent. The similarity in the pressure values indicates simply that the location and degree of circulatory congestion in the 3 categories of noncardiac circulatory congestion are the same as in congestive heart failure and verifies quantitatively the clinical finding of congestion in each. Subsequent data will examine

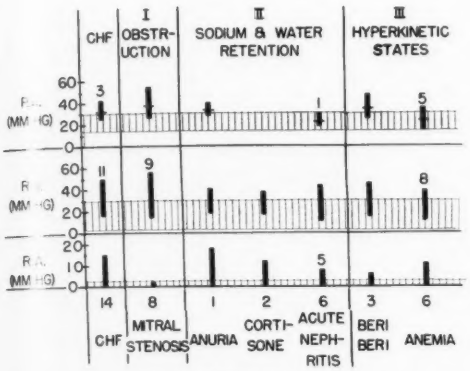

Figure 2

Comparison of intracardiac pressures in congestive heart failure and noncardiac circulatory congestion. At the top of each vertical panel is listed the category of circulatory congestion, at the bottom the individual disease states for each category. For pulmonary artery pressure (PA) and right ventricular pressure (RV) systolic pressure is plotted by the top and diastolic pressure by the bottom of the black columns. The short horizontal line through the pulmonary artery pressure column is mean pressure. Right atrial pressure (RA) is mean pressure plotted by the top of the black column. The tops of the horizontal, vertically hatched bands indicate maximum normal systolic pressure and the bottom of the bands maximum normal diastolic pressure. The numbers immediately below the abscissa indicate the number of subjects whose data have been averaged for each corresponding set of vertically arranged black columns. When a different number of subjects entered into a particular average, the number of subjects is now indicated by the number above the corresponding column.

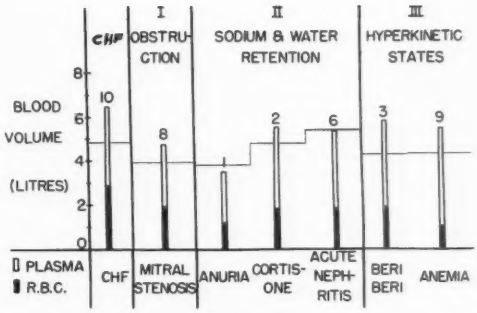

Figure 3

Comparison of blood volume in congestive heart failure and noncardiac circulatory congestion. (See legend figure 2 for manner and details of plotting.) Total blood volume is indicated by the height of the entire column, red cell volume by the solid portion, and plasma volume by the open portion of the column. The predicted blood volume (total) for each group of subjects is indicated by the corresponding horizontal line. The numbers above each column give the number of subjects whose data have been averaged for the value charted.

whether these similar circulatory congestions are associated with, and due to, the same or different hemodynamic causes.

With respect to blood volume in congestive heart failure, the total blood volume is usually,[5, 25-27] but not always,[28, 29] increased well above normal, and in the patients here studied averaged 30 per cent above predicted values (fig. 3). In the noncardiac circulatory congestions the blood volume was quite often not increased, and when it was increased the increments were frequently less marked than in congestive heart failure (fig. 3).

These data indicate that circulatory (venous) congestion, with elevated residual intracardiac pressures, may occur with no, or little, increase in total blood volume. Accordingly, blood volume is not the sole determinant of circulatory congestion. Vasoconstriction of all components of the vascular tree, specifically including the veins[30-33] and cardiac chambers, appears to be a very significant additional factor. Vasoconstriction is considered to contribute to the venous congestion in 2 ways: (1) by re-distributing blood from the minute vessels, essentially the venules, to the more distensible central collecting compartments, the large veins and atria and (2) by acting upon this increased local blood volume by an increase in venous tone. The result is an elevation in venous pressure and in intracardiac residual pressures.

The differences between congestive heart failure and noncardiac circulatory congestion become more fundamental when the more primary cardiac function of cardiac output is considered (fig. 4). Cardiac output is typically below normal in congestive heart failure [1-7, 34, 35] and, in contrast, essentially normal in the circulatory congestions associated with intracardiac obstruction and excessive

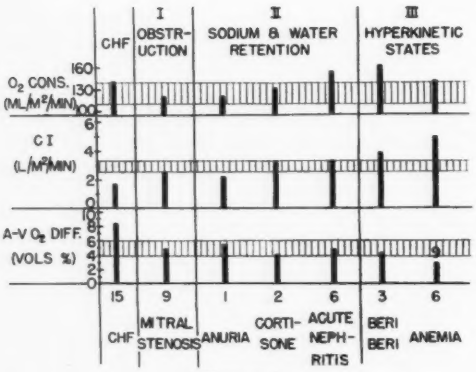

Figure 4

Comparison of cardiac output and its relation to oxygen consumption in congestive heart failure and noncirculatory congestion. (See legend figure 2 for manner and details of plotting.) Total oxygen consumption (O_2 Cons.), cardiac output as cardiac index (C.I.), and arterial-mixed venous oxygen difference (A-V O_2 Diff.) are indicated by the tops of the respective columns. The horizontal vertically hatched bands indicate, in this and subsequent charts, the range of normal values for the corresponding functions.

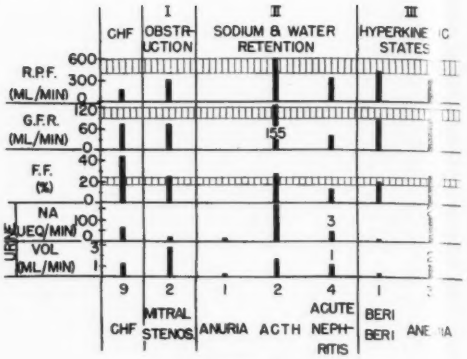

Figure 5

Comparison of renal hemodynamic functions and water and electrolyte excretions in congestive heart failure and noncardiac circulatory congestions. (See legends figures 2 and 4 for manner and details of plotting). Renal plasma flow (RPF), glomerular filtration rate (GFR), filtration fraction (FF), sodium excretion (Na), and water excretion (Vol) are indicated by the heights of the respective columns. Since the patients were not receiving a fixed salt and water intake, no normal range of water and electrolyte excretion is indicated.

water and salt retention, and typically high in beriberi and anemia. The arterial-mixed venous-oxygen difference, a better index of cardiac function since it relates the supply of blood (cardiac output) to the demand for it (oxygen consumption), further indicates the difference in cardiac function between cardiac and noncardiac circulatory congestions (fig. 4). In contrast to the typically high A-V oxygen difference in congestive heart failure are the normal values in the circulatory congestions due to intracardiac obstruction and water and salt retention and the low values in beriberi and anemia. These observations indicate that the first of the 3 proposed differences between noncardiac and cardiac congestion appears to be fulfilled, namely, a difference in cardiac function between the two states.

With respect to the proposed second criterion of difference, the circulation and function of peripheral organs, differences in renal hemodynamics were found between the two types of circulatory congestion (fig. 5). In congestive heart failure the markedly reduced renal plasma flow and the only moderately reduced glomerular filtration rate result in the strikingly increased filtration fraction, so characteristic of congestive heart failure[3, 6, 7, 36–39] In contrast, in the three categories of noncardiac circulatory congestion renal plasma flow and glomerular filtration rate were both more nearly normal and, of particular significance, the filtration fraction was not increased, or only very slightly so. Renal clearance measurements were not possible on the anuric patient. The low glomerular filtration rate and filtration fraction in glomerulonephritis results from the specific glomerular lesion in this disease. No data were obtained in patients with congested states due to salt-retaining hormones; the data following ACTH administration are for subjects without circulatory congestion and are included to indicate the type of effect produced on renal function by this hormone. Urinary excretions of water and electrolyte were variable and tended to be equally low in both types of congestion. Their significance is

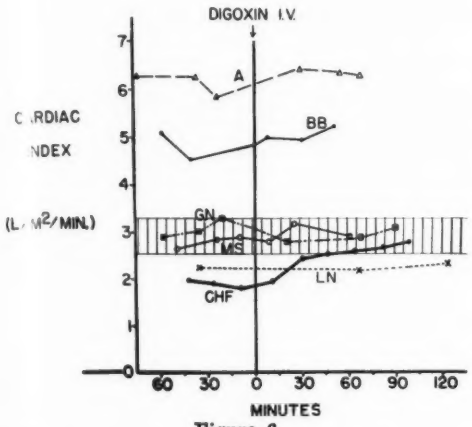

Figure 6

Comparison of the effect of intravenous digoxin on the cardiac output in congestive heart failure and noncardiac circulatory congestion. The vertical line indicates administration of a single, therapeutic dose of digoxin intravenously. The several lines connect points of individual determinations in the following types of patients: congestive heart failure (CHF), "pinch-cock" mitral stenosis (MS), anuria due to lower nephron nephrosis (LN), acute diffuse glomerulonephritis (GN), beriberi (BB), and severe anemia (A). The data for congestive heart failure are averages of 5 patients, all other data are for single subjects. The horizontal, vertically hatched band indicates range of normal values (From Transactions of the Association of American Physicians **67:** *72, 1954.)*

obscured by the varying salt and water intakes of the different patients. Taken as a whole, the data indicate that the second proposed criterion of difference between cardiac and noncardiac circulatory congestion appears fulfilled, at least for the kidney.

The proposed third criterion of difference between noncardiac and cardiac circulatory congestion requires a difference in response to specific medication. Digitalis is considered to return the abnormal hemodynamics of congestive heart failure to, or well toward, normal by a direct and specific effect on heart muscle. It is critical to the argument to determine whether digitalis has a similar, or different, effect in the noncardiac circulatory congestions. Accordingly, the hemodynamic effects produced by intravenously administered, single, therapeutic doses (1.0 mg. to

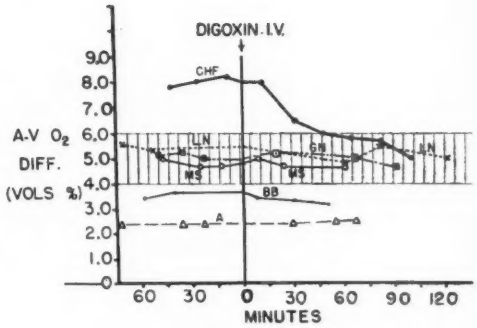

Figure 7

Comparison of the effect of intravenous digoxin on the arterial-mixed venous oxygen difference in congestive heart failure and noncardiac circulatory congestion. (See legend figure 6 for details of plotting.) (From Transactions of the Association of American Physicians **67:** *72, 1954.)*

1.5 mg.) of digoxin were determined. The digitalis glycoside produced no, or minimal, hemodynamic effects in the 3 types of noncardiac circulatory congestion, in contrast to prompt and decided improvement in hemodynamic functions in congestive heart failure (figs. 6-9).[1, 2, 4, 40, 41]

The cardiac output in congestive heart failure (CHF) increased from typically low values to normal levels within 1 to 2 hours after the intravenous administration of digoxin (fig. 6). In contrast, the normal cardiac ouput of "pinch-cock" mitral stenosis (MS) and glomerulonephritis (GN), the slightly lowered output of the anuric congestion (LN), and the high outputs of beriberi (BB) and anemia (A) all remained unchanged.

The response of the arterial-mixed venous oxygen difference following intravenously administered digoxin was likewise different in the 2 types of circulatory congestion and, as expected, reflected the changes in cardiac output (fig. 7). The abnormally high values in congestive heart failure fell to normal limits within 2 hours of administration of digoxin, whereas no changes occurred in the normal (MS, GN, LN) or low (A and BB) A-V oxygen differences of the noncardiac circulatory congestions.

In congestive heart failure the typically

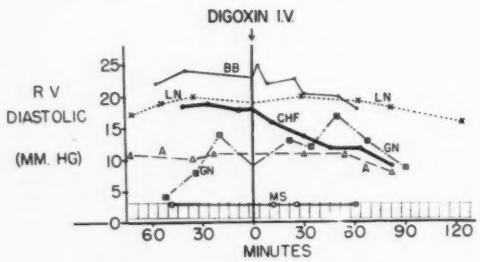

Figure 8

Comparison of the effect of intravenous digoxin on the right ventricular end-diastolic pressure in congestive heart failure and noncardiac circulatory congestion. (See legend figure 6 for details of plotting.) (From Transactions of the Association of American Physicians **67**: *72, 1954.)*

elevated intracardiac residual pressure, represented by the right ventricular end-diastolic pressure, was lowered markedly and characteristically, again within 1 to 2 hours, by intravenously administered digoxin.[42, 43] In the noncardiac circulatory congested states intravenous digoxin either did not affect this intracardiac pressure (GN, LN, A) or induced falls of smaller magnitude (BB) (fig. 8).

A prompt, considerable, and continuing diuresis of water and sodium was induced by the intravenously administered digoxin in congestive heart failure.[41, 44] Again in contrast, no increase in urine volume and a much smaller increase in sodium excretion followed the intravenous digoxin in 3 patients (LN, GN, and BB) with noncardiac circulatory congestion (fig. 9).

It is possible that single, intravenous doses of digitalis glycosides are not so optimally therapeutic as they are considered to be and that prolonged digitalis medication is required for full therapeutic effect. Accordingly, full digitalization, with digitalis leaf given orally, was carried out in some patients over several days. The results paralleled and substantiated the acute effects of therapeutic single doses of digoxin given intravenously: decided improvement in congestive heart failure, no, or equivocal, benefit in the 3 noncardiac congested states. For example, digitalis leaf in full therapeutic doses induced neither significant diuresis, weight loss, nor reduction of peripheral venous pressure in patient E. P. with severe hypochromic microcytic anemia and circulatory congestion (fig. 10). Ventricular premature contractions occurred after 3 days of fairly intensive digitalis medication, indicating adequate dosage of the drug, but the circulatory congestion remained largely unchanged and the patient desperately ill. Two transfusions were given. Diuresis, weight loss, and relief of circulatory congestion occurred as the erythrocyte concentration, following transfusion and iron medication, rose to normal values (fig. 10). Oral digitalization has also failed to induce a diuresis or relieve the venous congestion in acute glomerulonephritis, events which then followed spontaneous improvement in the disease process.

Similarly, beriberi heart disease failed to respond to digitalization, whereas the subsequent administration of thiamine produced an excellent diuresis.[45]

The differences in response to intravenous and oral digitalis appear to satisfy the proposed third criterion for separating noncardiac circulatory congestion from congestive heart failure.

The differences in general and local hemodynamic functions between congestive heart failure and the 3 categories of noncardiac circulation congestion make it difficult to accept for all states of circulatory congestion a common etiology of heart, that is myocardial, failure. Similar to both types of congested states are the clinical and hemodynamic evidences of circulatory congestion. But the congestion itself appears to be a secondary and nonspecific manifestation. Differences in the more primary hemodynamic functions separate the 2 types of circulatory congestion and offer the more reliable parameters of hemodynamic function to differentiate congestive heart failure, occurring in patients with diseased hearts, from noncardiac circulatory congestion, occurring in patients without intrinsic heart disease. Such a differentiation seems preferable to the common practice of grouping all circulatory congestions under the

single category of congestive heart failure, simply because of the presence of similar but nonspecific, clinical manifestations.

The following classification (table 2) is proposed:

Circulatory congestion, whether systemic or pulmonic, is itself a nonspecific hemodynamic manifestation and results from an increased central blood volume plus an increased vascular tonus. The increased central blood volume may be part of an increased total blood volume or the result of a redistribution of a more normal blood volume. The increased vascular tonus probably results from neurogenic and humoral responses. Circulatory congestion occurs when the heart is diseased, in which case the myocardium fails and the cardiac output falls. This is heart failure and results from failure of the heart's contracting force. This state should be differentiated from clinically similar circulatory congestions which occur under 3 types of circumstances: (1) when there is obstruction to blood flow in and about the heart, (2) when there is excess retention of water and salt, in both of which states the cardiac output is usually normal, and (3) in the hyperkinetic congested states, in which cardiac output is increased. In these states the heart appears not to fail as a pump and the circulatory congestion appears not to be of cardiac origin.

Such a differentiation of circulatory congestions is not a matter of semantics. An understanding of the different physiologic disturbances in the 2 types of circulatory congestion not only helps clarify the basic mechanisms of disease processes, but also finds practical application in proper therapy; digitalis benefits one, congestive heart failure, but is questionably effective in the other, the noncardiac circulatory congestions, in which states diuretic therapy is likely to be more effective. A practical consideration: the 2 types of circulatory congestion can often be differentiated by the simple bedside test of the circulation time. When properly performed, the circulation time correlates quite well with cardiac output: a decreased or normal circulation time indicating a high or normal cardiac output and hence a noncardiac congested state, an increased circulation time indicating a low cardiac output and congestive heart failure. Also, it should be recognized that noncardiac circulatory congestion is much less frequently encountered than congestive heart failure and that combinations of the 2 types of congestion may occur in the same patient. The data presented have dealt with carefully chosen instances of typical, uncomplicated, noncardiac and cardiac circulatory congestions. Excluded from consideration were combinations of the 2 states in which the physiologic disturbances partake, in varying degrees, of each; for example, occluding mitral stenosis associated with left ventricular failure and a large heart, or exacerbation of acute nephritis in a patient with chronic nephritis and hypertension, which has caused some left ventricular failure as well.

Table 2

Circulatory (Venous) Congestion
(Increased central venous blood volume plus increased vascular tone)

I.	*Cardiac*	
	Congestive heart failure	low cardiac output
II.	*Noncardiac (nonmyocardial)*	
	Cardiac mechanical obstruction	normal cardiac output
	Excessive water and salt retention	normal cardiac output
	Hyperkinetic congested states	high cardiac output

Effect of Circulatory Congestion on Cardiac Function and Renal Function

Let us turn now to the second area for consideration, the effect of circulatory (venous) congestion itself on cardiac, hemodynamic, and renal functions. Sobol, Kessler, and Rader[46] measured the changes in these functions when circulatory congestion was decreased by means not involving the heart. A steady state of primary, peripheral vasodilatation was produced for 1 hour by the controlled, continuous, intravenous infusion of the ganglion-blocking agent, Arfonad. Arfonad was chosen because it has a periph-

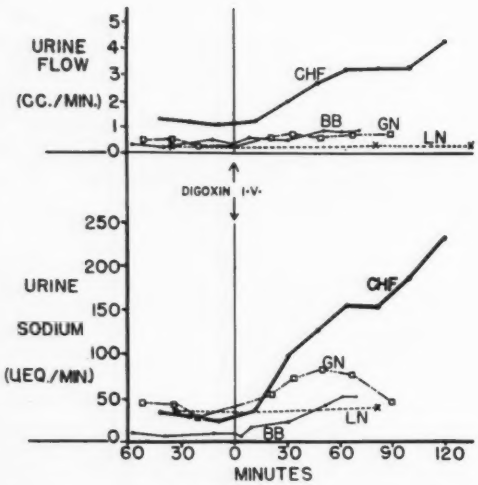

Figure 9

Comparison of effect of intravenous digoxin on water and sodium excretions in congestive heart failure and noncardiac circulatory congestion. (See legend figure 6 for details of plotting.) No band of range of normal values is indicated since the patients were not receiving a fixed salt and water intake. (From Transactions of the Association of American Physicians **67:** *72, 1954.)*

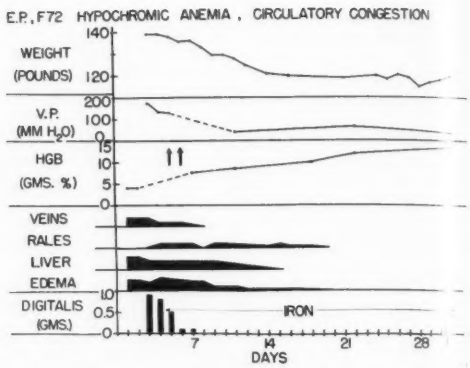

Figure 10

Ineffectiveness of oral digitalis therapy in circulatory congestion associated with severe anemia. Each vertical arrow in the horizontal panel HGB indicates transfusion of 500 ml. of blood. The height of the horizontal panels Veins, Rales, Liver, Edema represent 4+. VP, venous pressure; HGB, hemoglobin.

eral effect, and no direct effect upon the heart as a whole or on the heart muscle cell has been demonstrated.[47, 48]

Measurements of circulatory, cardiac, and renal function were obtained during a control period, throughout the hour of vasodilatation, and finally when the circulation had returned to its initial state following cessation of the infusion.

In both normotensive and hypertensive subjects in congestive heart failure, right atrial pressure and right ventricular end-diastolic pressure, indices of circulatory congestion behind the right heart, and pulmonary artery pressure and right ventricular systolic pressure, indices of circulatory congestion behind the left heart, decreased and remained decreased during the period of vasodilatation, then returned to the initial level after the infusion (fig. 11).[46, 49–52] The pressures did not, however, fall to the normal range. Similarly, these pressures fell, but remained within the normal range, in a control group composed of noncardiac subjects and hypertensive and normotensive cardiac subjects compensated from congested heart failure.[49, 53–55] The decrease in cardiac filling pressures could not be achieved with this agent without a concomitant fall in systemic arterial pressure. The degree of reduction of systemic pressure was so controlled, however, that the lowered pressure did not fall outside the normal range (fig. 11).

Associated with the fall in intracardiac residual pressures, and reduction in the congested state, cardiac output increased in the patients with congestive heart failure,[46, 49, 53, 54] presumably as a result of the decrease in ventricular filling pressure (fig. 12). After the dilatation, as intracardiac residual pressure rose, cardiac output fell to the initial level. The rise in cardiac output was small, averaged 15 per cent, and did not carry the output into the normal range. This small increase becomes more significant, however, when contrasted with the fall in cardiac output, to below the normal range, which occurred during the period of decreased ventricular filling pressure in the control noncardiac and compensated cardiac subjects (fig. 12).[46, 53–55]

The significance of the rise in cardiac out-

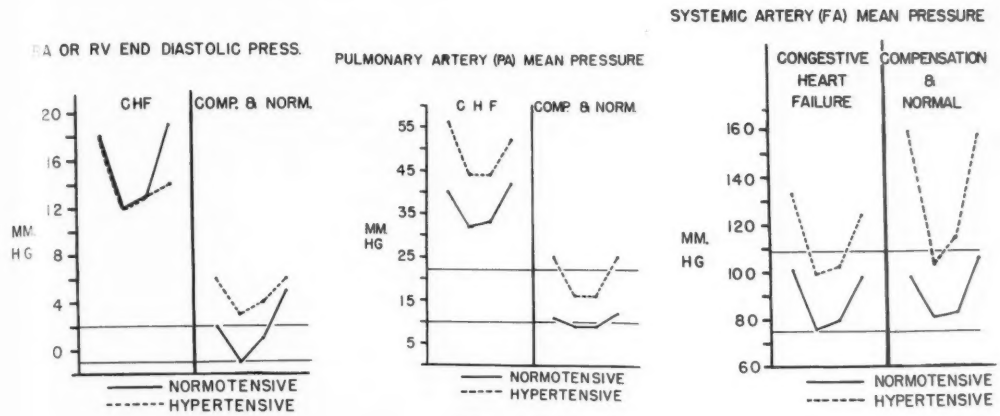

Figure 11

Effect of vasodilatation, produced by intravenous infusion of ganglion-blocking agent (Arfonad), on intracardiac and vascular pressures in congestive heart failure (CHF) and in nonfailing circulation (Comp. & Normal). The data are averages for the following groups: Congestive heart failure: normotensive, 5 patients; hypertensive, 5 patients. Nonfailing circulation: normotensive, 2 noncardiac subjects and 1 patient recovered from congestive heart failure; hypertensive, 2 patients recovered from congestive heart failure. For each line the first point gives the average of the data of 2 or 3 control periods, the second point gives the maximum effect during vasodilatation, the third point gives the average of the data of 2 or 3 observations during 1 hour of vasodilatation, the fourth point gives the data of the post-vasodilatation or recovery period. The 2 horizontal lines in each panel indicate the range of normal values. RA, right, atrium; RV, right ventricle.

put in congestive heart failure during the period of reduction of the elevated ventricular filling pressure, was substantiated by a concomitant and sizable fall (average 22 per cent) in arterial-mixed venous oxygen difference and by its rise to control levels in the postdilatation period after stopping the Arfonad infusion (fig. 12). Furthermore, an increase (small) in oxygen content of mixed venous blood paralleled the fall in A-V oxygen difference and thus further indicated that cardiac function had improved. Witness also, the contrasting behavior of the A-V oxygen difference in the noncardiac and compensated control subjects, a small increase or no change.

These experiments suggest that circulatory congestion of itself may have an undesirable effect upon cardiac function, increased congestion acting to reduce the cardiac output, which then rises as the congestion is removed. The observations, however, are complex, for systemic arterial pressure also fell. The increased cardiac output may, therefore, be merely a manifestation of an increase in output against a lessened external resistance, and not a function of improved myocardial contraction resulting from decreased central circulatory congestion.

The increase in cardiac output during lowering of the elevated ventricular filling pressure in congestive heart failure and the contrasting decrease in cardiac output during lowering of the normal filling pressure in noncongested states suggests that Starling's law[56–58] of the heart applied in intact man. Unfortunately, the falls in systemic and pulmonic arterial pressures make such a conclusion debatable. Since cardiac work is the product of cardiac output and the pressure against which the output is ejected, the increase in cardiac output, which occurred when ventricular filling pressure was lowered in congestive heart failure, is offset by the associated lowering of the arterial pressures.

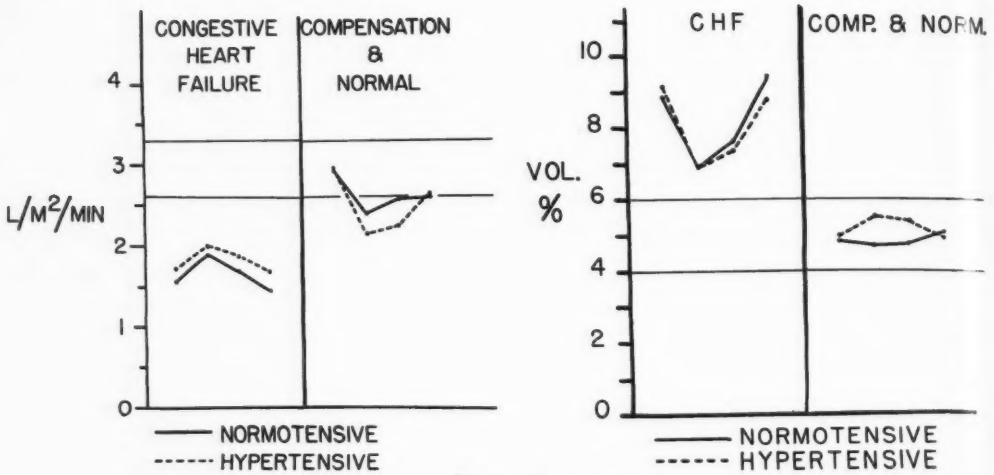

Figure 12

Effect of vasodilatation, produced by intravenous infusion of ganglion-blocking agent (Arfonad), on cardiac output (left) *and arterial mixed venous oxygen difference* (right) *in congestive heart failure (CHF), and in nonfailing circulation (Comp. & Normal). Details of plotting are the same as in figure 11.*

Accordingly, minute work and stroke work of the heart, both of the left and right ventricle, and in both hypertensive and normotensive subjects, did not change as the central filling pressure fell (fig. 13). In the noncongested states minute and stroke work decreased as filling pressures fell. Such an analysis would indicate that Starling's law of the heart held for normal states but did not maintain in the failing heart with a congested circulation. Nevertheless, an interesting hemodynamic state was produced, wherein a heart, perhaps incapable of greater work, was able to deliver more blood to the circulation and thereby meet more fully the needs of the peripheral organs and of the body as a whole. It is not intended here to suggest that these acute short time events are applicable to long-term maintenance medication with vasodilating agents. Reports in the literature indicate beneficial results from such an approach[59] but further observations and analysis are required, particularly in view of the reduced water and electrolyte excretions that occurred during the period of reduced pressures.[46, 60, 61]

Because Arfonad produced a hemodynamic state that did not lend itself to a rigid test of Starling's law of the heart, Ziffer and Rader[62] repeated studies of this type using sodium nitrite to obtain reduction of circulatory congesting pressure. The advantage of sodium nitrite is that it acts chiefly upon the postarteriolar, that is the venous, segment of the circulation and hence is less likely to lower arterial pressure in the supine subject.[63, 64] This drug also has no direct cardiac effect. Accordingly, 0.1 to 0.2 Gm. of the drug was given by mouth and within 15 minutes the right atrial and right ventricular end-diastolic pressures were decreased, without a lowering of the arterial pressures by more than 5 to 10 mm. Hg. The pressure changes persisted for about 1 hour and were gone by 2 hours after ingestion of the drug.

Under these conditions of decreased circulatory congestion and lowering of the elevated ventricular filling pressures of congestive heart failure the cardiac output again increased (fig. 14). Since the changes in arterial pressure and heart rate were very small, minute work and stroke work of the ventricles obviously increased. Again in contrast, in subjects without circulatory congestion, car-

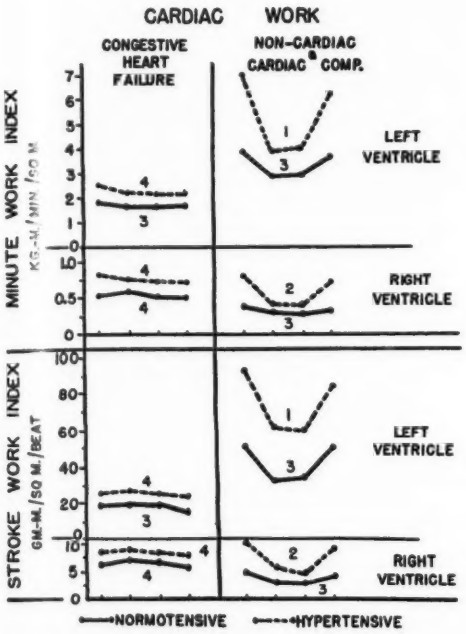

Figure 13

Effect of vasodilatation, produced by intravenous infusion of ganglion-blocking agent (Arfonad), on cardiac work in congestive heart failure (CHF), and in nonfailing circulation (Comp. & Normal). Details of plotting are the same as in figure 11, except that the horizontal line separates the data for the 2 ventricles and not the range of normal values. The numbers indicate subjects averaged for the corresponding data charted. (From Journal of Clinical Investigation **38**: *557, 1959.)*

diac output, minute work, and stroke work all decreased when normal filling pressures were lowered (fig. 15). Starling's law of the heart appeared, therefore, to apply in both the circulatory congestion of heart failure and the noncongested noncardiac or compensated cardiac states.

Since there were in both types of observation no means of knowing the changes, if any, in cardiac fiber length, the ultimate applicability of Starling's law may still be questioned. It is, however, worth considering whether the most significant parameter of the cardiac muscle fiber with respect to its contractile force is, not its length, but the *tension* within the fiber. Tension would con-

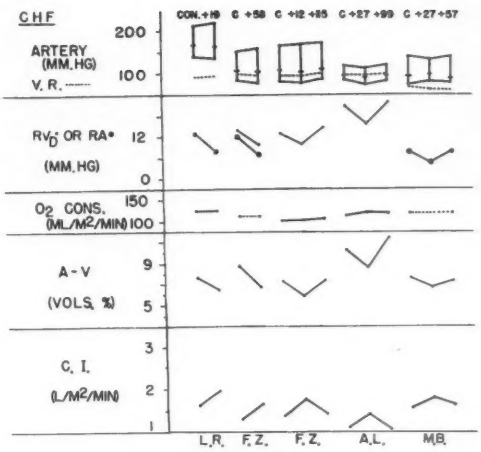

Figure 14

Effect of vasodilatation, produced by oral sodium nitrite, on cardiovascular dynamics in congestive heart failure. The data are arranged vertically for each of 4 subjects represented by initials along the abscissa (subject F.Z. was studied in 2 bouts of congestive failure). For each subject the first point indicates the average of control observations (C at top), the second point gives the data during maximum vasodilatation occurring at a time after ingestion of $NaNO_2$ indicated by the first "plus number" at the top, the third point (when present) gives the data after return to the control state at the time after ingestion of $NaNO_2$ indicated by the second "plus number" at the top. Artery = systemic arterial pressure, vertical line connects systolic and diastolic pressure, horizontal dash gives mean pressure; VR = ventricular rate; RV_d = right ventricular end diastolic pressure, solid dot; RA = right atrial mean pressure, open circle; O_2 Cons. = total oxygen consumption; A-V = arterial-mixed venous oxygen difference; C.I. = cardiac index.

stitute the force governing the arrangement of the ultrastructural components of the contractile protein of the myocardial cell[65] and this arrangement could well be the ultimate factor determining the subsequent contraction of the fiber. This line of reasoning lends support to the many observations that have related cardiac function to filling pressure, and Starling's observations,[56, 57] as well as Frank's,[66] dealt with this parameter.

At any rate, the observations do indicate that circulatory congestion, with its associated increased intracardiac residual pressures, has

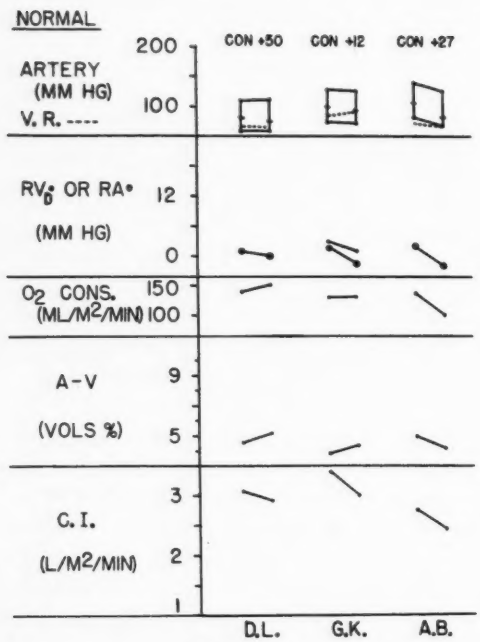

Figure 15

Effect of vasodilatation, produced by oral sodium nitrite, on cardiovascular dynamics in nonfailing circulation. Details of plotting are the same as in figure 14.

the deleterious effect of decreasing the cardiac output and work of the diseased heart, and that relief of the congestion may be expected of itself to improve the function of such hearts.

Consider now the effect of venous congestion itself on the circulation and function of peripheral organs and again the kidney was chosen for study.

Farber and Becker[67, 68] produced, in noncardiac subjects, congestion of any desired segment of the vena caval vascular bed, both including and excluding the kidney. A catheter, equipped with a balloon, which could be inflated with Diodrast solution, was placed in the superior vena cava or in the inferior vena cava above or below the renal veins. By gradual inflation of the balloon, distal venous pressure was raised to 150 mm. to 250 mm. of water, levels similar to those in congestive heart failure. The venous congestion was maintained for 30 to 50 minutes, without knowledge or discomfort to the subject, without change in arterial pressure and, in the few instances measured, without change in cardiac output. Renal functions were then determined before, during, and after inflation of the balloon.

In these noncardiac subjects, congestion of the inferior vena caval drainage area, including the kidneys, produced prompt decreases in urine output and in the excretion of sodium and potassium (fig. 16).[68] Arterial pressure remained essentially unchanged. Renal plasma flow and glomerular filtration rate were reduced immediately upon inflation of the balloon but returned well toward control levels as the congestion was maintained. Nevertheless, decreased water and electrolyte excretion continued throughout the period of congestion. Following deflation of the balloon and relief of venous congestion all functions returned to the control level.[69–73]

Congestion of the kidney was not essential to the decreases in water and electrolyte excretion. Congestion of the inferior vena cava below the renal veins induced similar decreases in urine flow and in sodium excretion, with no, or minimal, change in renal blood flow and glomerular filtration (fig. 17).[68, 74, 75] Furthermore, congestion of the superior vena caval drainage area also produced decreases in water, sodium, and potassium excretion, again without significant change in blood pressure, renal blood flow, or glomerular filtration (fig. 18).[68, 76] Unlike the response to inferior vena caval congestion, the reduced water and electrolyte excretions occurring during congestion of the superior vena cava appeared to endure beyond the period of venous congestion and persisted after deflation of the balloon.

These observations indicate that venous congestion of itself, at least apart from systemic arterial pressure and renal blood flow, acts to decrease the excretion of water and electrolytes. Furthermore, this effect does not require congestion of the kidney but appears to be related to the size of the vascular bed that is congested. When the kidney is in-

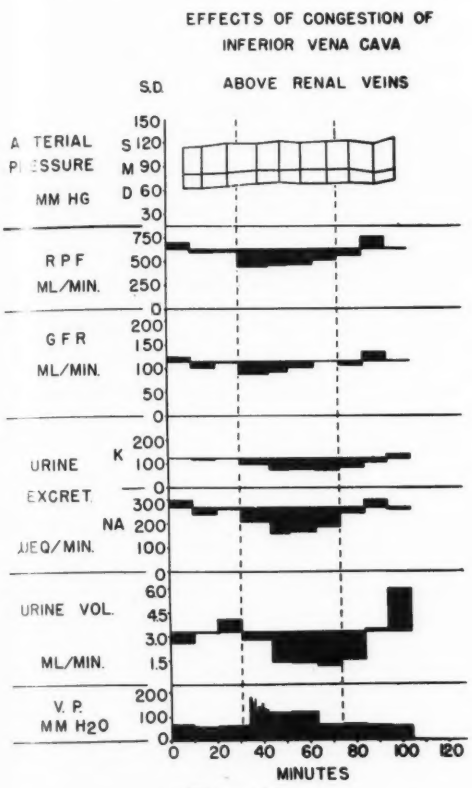

Figure 16

Effect of inferior vena caval congestion, including renal veins, on renal hemodynamic functions and water and electrolyte excretions; representative response. Vena caval congestion was induced by inflating a balloon in the inferior vena cava above the renal veins. The dotted line on the left indicates inflation of the balloon and the dotted line on the right deflation of the balloon. Vena caval pressure (V.P.) peripheral to the inflated balloon and systemic arterial pressure are plotted as determined values above zero. Renal plasma flow (RPF), glomerular filtration rate (GFR), and excretions of potassium (K), sodium (Na), and water (Vol.) are plotted, for each 10- to 15-minute period, as changes from the average of their respective 3 control determinations. (From Journal of Clinical Investigation **32:** *1145, 1953.)*

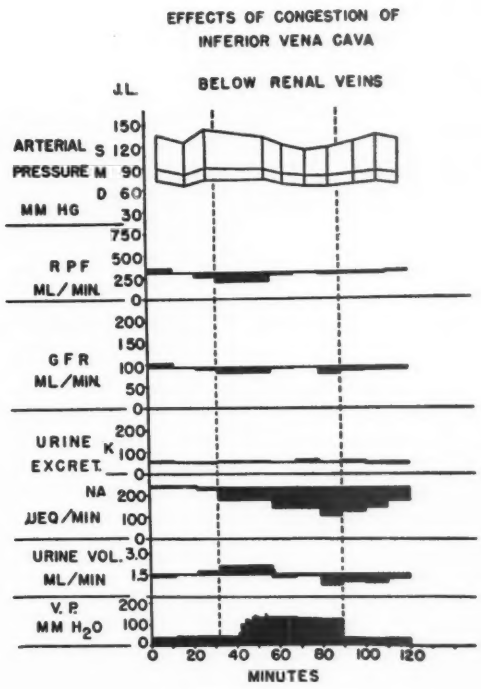

Figure 17

Effect of inferior vena caval congestion, excluding renal veins, on renal hemodynamic functions and water and electrolyte excretions; representative response. Details of plotting are the same as in figure 16. Vena caval congestion was induced by inflating a balloon in the inferior vena cava below the renal veins. (From Journal of Clinical Investigation **32:** *1145, 1953.)*

volved in the congested area, the effect is more pronounced.

The question obviously arises, whether these changes in circulation, cardiac function, and renal function, resulting acutely as they did during relatively short periods of alteration in circulatory congestion, have any significance with respect to long-term effects in clinical congestive heart failure. Rader, Berger, and Smith[77] have determined the hemodynamic effects resulting from long-term relief of venous congestion in patients with congestive heart failure. The aim was to relieve the venous congestion by noncardiac means. Control hemodynamic measurements were made on patients who had not received digitalis or diuretic therapy for at least 1 month and who were in typical, low-output congestive heart failure. Mercaptomerin, a mercurial diuretic considered to have no intrinsic cardiac effect, since the mercury is stabilized

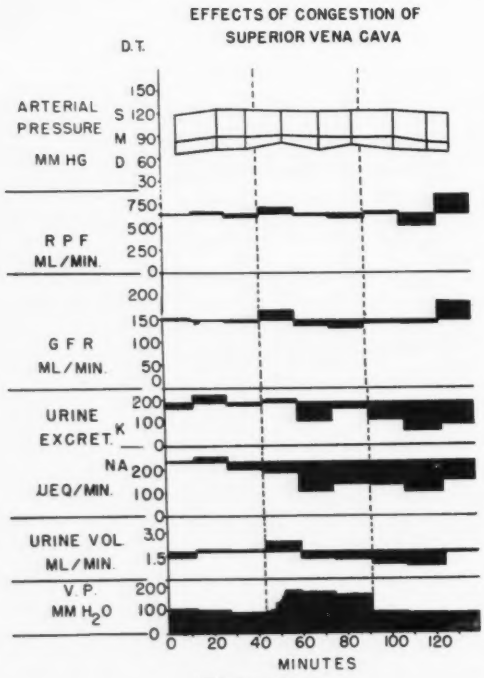

Figure 18

Effect of superior vena caval congestion on renal hemodynamic functions and water and electrolyte excretions; representative response. Details of plotting are the same as in figure 16. Vena caval congestion was induced by inflating a balloon in the superior vena cava just proximal to its entrance into the right atrium. (From Journal of Clinical Investigation **32:** *1145, 1953.)*

with sulfhydryl and hence avoids the possible cardiotonic effect of the xanthines used in stabilizing meralluride, was then administered repeatedly until the circulatory (venous) congestion had disappeared and the patient was edema-free and subjectively essentially recovered. Hemodynamic measurements were then repeated, usually 2 to 3 weeks after the initial measurements, to determine the effects of removal of the circulatory congestion. Digitalis leaf was next given orally until full digitalization was achieved, when a third set of measurements was made, now to determine whether the cardiotonic effect of this drug produced any hemodynamic effect beyond that obtained by relief of venous congestion by diuretic medication.

In all instances mercurial diuresis relieved the circulatory congestion, lowered the venous pressure to normal, and often returned right ventricular end-diastolic pressure and right atrial pressure to normal levels.[77, 78] All patients were improved, usually to the extent that they could be considered clinically compensated. In half of the subjects, generally patients in their first or second episode of congestive failure, cardiac output rose,[77, 78] often considerably, as the congested state was relieved, and digitalization produced no further change in subjective improvement, vascular and cardiac pressures, or cardiac output (fig. 19). Relief of the venous congestion itself had effectively returned cardiac function toward normal. In a sense this result may be interpreted as an indication of the Starling law effect in a chronic situation.

In the remaining half of the subjects, usually in a repeated episode of congestive failure due to neglect to take medication, mercurial diuresis removed equally well the circulatory congestion, reduced the residual cardiac pressures, removed the edema, and produced equal subjective improvement in the patient, but cardiac output did not rise above that determined during congestive heart failure. Full doses of digitalis leaf now produced an increase in cardiac output, indicating in these subjects a cardiotonic effect improving cardiac function (fig. 20). Finally, in a third group of subjects, usually in chronic congestive heart failure with repeated decompensation developing quickly after lapse of therapy, cardiac output did not rise when venous congestion was removed by either diuretic or digitalis therapy, or both. Subjective improvement followed removal of the circulatory congestion, however, regardless of lack of improvement in cardiac function and cardiac output.

The observations thus far discussed clarify the relationship of symptoms to the congested state on the one hand and to cardiac output on the other. It is apparent that the classical manifestations of congestive heart failure, the dyspnea, orthopnea, tachypnea, tachycardia, venous distention, and edema are man-

ifestations of circulatory congestion and not of the cardiac output itself. Circulatory congestion produces the symptoms regardless of whether the cardiac output is low, or high or normal. Once the congestion is removed, the patient is relieved of these manifestations, again regardless of whether the cardiac output remains high, low, or returns to normal. An interesting example of this relationship is indicated by patient C. McC. (fig. 21). Severe mitral stenosis had markedly curtailed her activity to the point that she suffered from incipient and overt pulmonary edema and required oxygen inhalation equipment for home use to secure relief. Her high pulmonary artery pressure (61/32 mm. Hg) indicated the severity of the pulmonary congestion. A mitral commissurotomy relieved the pulmonary congestion, as evidenced by the fall of pulmonary artery pressure to normal. With relief of the circulatory congestion respiratory distress disappeared and the patient discarded her now useless oxygen inhalation equipment. Two years after operation the cardiac output was found to be unchanged and just as low after operation as before it,[79] both at rest and on exercise (fig. 21). And yet the patient had become normally active without symptoms and without developing congestive failure. She did, however, continue digitalis therapy.

Relief of symptoms, with persistence of a low cardiac output, is a common occurrence today in cardiac patients when judicious use of digitalis and diuretics prevents the development of circulatory congestion. Increased extraction of oxygen, and perhaps other substances, from the blood appears to constitute an effective mechanism compensating for poor myocardial activity and decreased blood flow. The lowered cardiac output, however, accounts for a very important symptom in heart failure, namely, fatigue, particularly on exertion. Too often a patient is considered "compensated" from heart failure because the objective and subjective manifestations of circulatory congestion have been removed, often by noncardiac medication, while the actual state of heart failure remains unrecognized in the fatigue and dyspnea that exertion induces. It

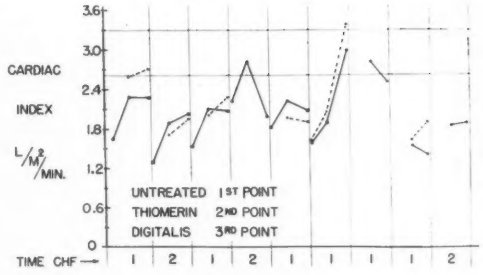

Figure 19

Comparison of effect of mercurial diuretic therapy and digitalis therapy on cardiac output in congestive heart failure. Plotted are subjects in whom cardiac output increased following diuretic therapy, without (generally) further increase following digitalis therapy. Each vertical panel represents 1 patient in congestive heart failure for the time represented by number below abscissa. The 2 horizontal lines encompass the normal range of values. Solid lines indicate values obtained during resting state, dotted lines during exercise. For each patient the first point indicates values during untreated congestive heart failure, the middle point indicates values after mercurial diuresis to "dry weight," the third point gives values following full digitalization carried out after the diuretic therapy. Panels with only 2 points give data after mercurial diuresis and digitalis therapy respectively, data during untreated congestive failure were not obtained in these patients.

is necessary to recognize and to give greater significance to the manifestations of fatigue as evidences of heart failure, and not to rely solely upon the nonspecific manifestations of circulatory congestion.[80]

Lowered Cardiac Output and Survival

The third area to be considered concerns the relationship of cardiac output to activity and survival, after the onset of congestive heart failure. A continuing study is correlating long-term, follow-up hemodynamic measurements with clinical observations on patients recovered from acute congestive heart failure and maintained on digitalis and, when necessary, diuretic medication. The still insufficient data suggest that the duration of survival seems less dependent on the level of cardiac output than on elevation of intracardiac pressures. Patients recovered from their *first* episode of congestive heart failure and receiving

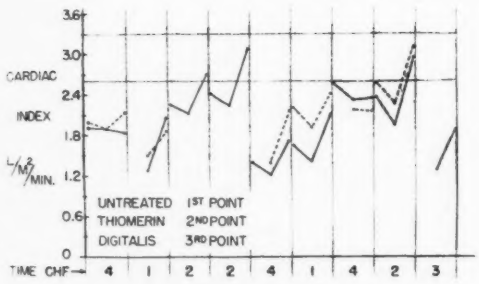

Figure 20

Comparison of effect of mercurial diuretic therapy and digitalis therapy on cardiac output in congestive heart failure. Plotted are subjects in whom cardiac output failed to change after diuretic therapy, with increase in output following subsequent digitalis therapy (except for subjects in chronic heart failure with fixed low cardiac output). Details of plotting are the same as in figure 17.

maintenance digitalis therapy undergo hemodynamic determinations and are grouped by calendar years. The initial hemodynamic data and follow-up data of subjects surviving 5 years or longer are compared with similar data derived from patients dying in less than 5 years. There is little to choose between the 2 groups with respect to age or a series of hemodynamic factors, including total oxygen consumption, blood volume, arterial oxygen content and saturation, systemic arterial pressure, right atrial pressure, right ventricular end-diastolic pressure, cardiac output, and A-V oxygen difference. Certainly long survival has been consistent with low cardiac outputs and high A-V oxygen differences, attesting again the satisfactory homeostasis of increased oxygen extraction from blood in compensating for a lowered cardiac output. The one hemodynamic measurement that seems to separate the 2 groups is the level of right ventricular systolic, and pulmonary arterial, pressure: subjects in whom right ventricular pressure was elevated (systolic pressure in excess of 45 mm. Hg) usually died within 5 years of the onset of congestive failure, whereas subjects with lowest right ventricular pressures (normal range) have led fairly asymptomatic lives for 5 to 9 years. Why elevation of right ventricular pressure should have an adverse effect is not clear. It is established, however, that oxygen uptake by the myocardium is not so much a factor of the external work performed as it is a function of the tension that the myocardium is required to sustain.[85, 86] Obviously, then, the load on the myocardium is greater when hypertension is present.

Furthermore, patients may sustain low, and even very low, cardiac outputs for a number of years without signs or symptoms of circulatory congestion or fatigue on effort. The progressively decreasing cardiac output with aging is well known.[87, 88] In the aged, cardiac output is often reduced to levels as low as those in congestive heart failure, yet circulatory congestion does not develop. Serial hemodynamic data on a representative cardiac subject, now followed for 10 years, illustrate the paradox of low cardiac output associated with excellent activity (fig. 22). The patient initially presented with congestive heart failure which responded to digitalis and he became asymptomatic and edema free. He remains so and still takes digitalis. The unusual feature is the exertional activity that this man undertakes without symptoms. Over the 10 years he has continued to walk a great deal and prides himself on walking 30 to 50 city blocks and up 6 to 8 flights of stairs, all without stopping, dyspnea, or fatigue. During this period his cardiac output has remained in the range of severe congestive heart failure, 1.70 to 2.0 L./M.^{2}/min. Even though circulatory congestion may have been removed by the medication taken, the level of cardiac output is so low that fatigue and dyspnea would be expected. It is important that the right ventricular pressure has remained essentially normal over 9 years. Here, then, is the paradox, why do circulatory congestion and exertional fatigue develop in one group of subjects but are absent in another group—both with apparently equally low cardiac outputs? No explanation is apparent for this discrepancy and since this discussion has been presented from the standpoint of the primary significance of cardiac output in congestive heart failure, the paradox is not a satisfying

	BEFORE OPERATION		AFTER OPERATION	
	REST	EXERCISE	REST	EXERCISE
PA MM HG	61/32	64/40	20/8	22/8
RV MM HG	60/5	—	20/3	25/4
RA MM HG	6	—	2	—
BA MM HG	139/71	143/66	137/66	156/73
O_2 CONS. ML/M²/MIN	120	267	109	214
BA O_2 VOLS %	16.03	16.89	18.68	18.77
PA O_2 VOLS %	9.90	6.13	12.63	9.38
A-V O_2 VOLS %	6.13	10.76	6.05	9.39
CI L/M²/MIN	1.95	2.47	1.81	2.29

Figure 21

Effect of mitral commissurotomy on cardiovascular dynamics in patient (C.McC., a 49-year-old woman) with severe mitral stenosis. The postoperative data were determined 2 years after operation.

DATE	1949	1950	1952	1955	1958
DEGREE CHF	2+	0	0	0	0
MEDICATION	NONE	← DIGITALIS →			
O_2 CONS. ML/M²/MIN	124	117	104	111	115
FA O_2 VOLS.%	12.61	15.18	17.00	16.68	16.69
PA O_2 VOLS.%	5.04	8.73	10.90	10.34	10.96
A-V O_2 VOLS.%	7.57	6.45	6.10	6.34	5.74
C.I. L/M²/MIN	1.64	1.81	1.70	1.75	2.06
PA MM HG	35/16	38/16	24/10	32/14	—
RV MM HG	37/13	34/8	20/5	33/11	—
RA MM HG	12	6	4	9	10
FA MM HG	132/88	137/77	128/65	153/83	113/65

Figure 22

Cardiovascular dynamics over course of 9 years in patient (W.G., a 71-year-old man) with arteriosclerotic heart disease. Initial congestive heart failure in 1949 responded to digitalis. Maintenance digitalis therapy continued thereafter.

one at which to arrive. It is, nonetheless, a paradox at which our present information brings us.

Speculation into the future may not be amiss at this point. In consideration of heart failure the clinician has traditionally equated heart failure with circulatory, that is venous, congestion. The observations here presented indicate that the two are not synonymous. More recently, hemodynamic measurements have tended to equate heart failure with either low cardiac output or low cardiac external work, parameters that are concerned with what the heart does for the total circulation, for the body as a whole. This function of the heart is obviously important, for upon it depends the survival of the total organism and from its inadequacy follow such abnormal circulatory phenomena as circulatory congestion. Focus upon the external work of the heart, however, loses sight of myocardial cellular events. It is apparent that for a given external work accomplished, myocardial cellular metabolism may be relatively normal or very abnormal, depending upon different situations of cardiac output and the pressure against which the output is delivered.[81-86] After all, the myocardium is a muscle and it is an anatomic happenstance that its contraction expresses blood, physiologically vital though that blood may be for the organism. But with respect to the heart muscle itself, it is the intrinsic cellular metabolism, and that metabolism alone, which determines whether the heart is contracting normally or is failing. The relationship between myocardial tension and oxygen utilization, suggested by both animal experiments and clinical experience in man, indicates a fruitful area of investigation in the problem of heart failure. It is trite to say that cellular biochemical relationships will resolve the problems of the failing heart, for they will. Until that day, it is well for the clinician and the physiologist to begin considering the patient with heart disease not from the standpoint of circulatory congestion nor cardiac output and cardiac external work, but from the standpoint of the myocardial cell and its metabolism. Clues to that metabolism should be sought, not only in experimental determinations, but also at the clinical level. Such clues may give a better indication, than congestion or output, of cardiac function and indicate whether the heart muscle is normal or failing, and failing badly or mildly. Certainly new parameters are required to indicate the true status of the heart in many clinical situations, for example, the noncongested cardiac patient vigorously treated with digitalis and diuretics, severe cardiac failure without congestive changes, the tachycardias, sudden heart failure, and retention of activity in spite of low output.

In recapitulation, and in closing, several points seem clear: (1) Circulatory (venous) congestion is the hemodynamic disturbance responsible for the symptoms usually associ-

ated with congestive heart failure; removal of the congestion, regardless of how accomplished, relieves the symptoms. (2) Circulatory congestion is a nonspecific hemodynamic disturbance and may arise when the heart does not fail as a pump. This is noncardiac circulatory congestion. (3) The term congestive heart failure should be reserved for those states of circulatory congestion in which there is myocardial failure. (4) Circulatory congestion of itself has undesirable effects on the heart and impairs cardiac function when the heart muscle is already involved. (5) Circulatory congestion of itself affects the kidney to impair its function in excreting salt and water. (6) A low cardiac output is a preferred indicator of heart failure and is the function responsible for the symptoms of exertional dyspnea and fatigue, often overlooked as symptoms of heart failure. Less clear-cut points are (7) Starling's law of the heart appears to hold in intact man in both the congested and noncongested circulatory states. (8) A low cardiac output is consistent with survival for years and appears to carry a less dangerous prognostic significance than elevation in ventricular pressures. A totally unclear and paradoxical point relegated for future resolution is, (9) the relationship of low cardiac output to adequate activity on the one hand and congestive heart failure on the other. A speculation (10) would indicate that in the future heart failure will be considered not from the standpoint of resultant gross manifestations (circulatory congestion) or external work performed by the heart (cardiac output and cardiac work) but from the standpoint of intrinsic myocardial metabolism, regardless of what the clinical manifestations or external cardiac work may be.

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Summario in Interlingua

Le conferentiario recapitulava su presentation in le sequente punctos:

1. Congestion circulatori (i.e. venose) es le disturbation hemodynamic responsabile pro le symptomas que es usualmente associate con congestive disfallimento cardiac. Le resolution del congestion— sin reguardo al natura del mesuras usate—allevia le symptomas.

2. Congestion circulatori es un nonspecific disturbation hemodynamic que pote occurrer sin que le corde manifesta ulle dysfunction in su labor de pumpa. In tal casos le congestion circulatori es noncardiac.

3. Le termino "congestive disfallimento cardiac" deberea esser reservate al statos de congestion circulatori in que il existe un disfallimento myocardial.

4. Le presentia de congestion circulatori per se produce effectos adverse in le corde e resulta in un vitiation del function cardiac si le musculo del corde es jam afficite.

5. Congestion circulatori per se affice le renes con le resultato de dysfunction del mechanismo renal de excretion de sal e aqua.

6. Un basse rendimento cardiac es un excellente indicator de disfallimento cardiac. Illo es le causa responsabile pro le symptomas de dyspnea post effortio e de fatiga (que es frequentemente negligite como manifestationes de disfallimento cardiac.

7. Il pare que le lege del corde, formulate per Starling, es valide in le homine intacte in stato circulatori tanto congestionate como etiam non congestionate.

8. Un basse nivello del rendimento cardiac es compatibile con le superviventia del patiente durante longe annos. Illo pare esser minus hasardose ab le puncto de vista del prognose que un nivello elevate del tension ventricular.

9. Un question ancora completemente obscur e paradoxe concerne le relation inter basse rendimentos cardiac e le duple possibilitate de activitate adequate o congestive disfallimento del corde. Iste question debe esser resolvite in le futuro.

10. Il es permittite specular que in tempores veniente le disfallimento del corde va esser considerate minus ab le puncto de vista del resultante manifestationes grossier (i.e. le congestion circulatori) o ab le puncto de vista del externe travalio effectuate per le corde (i.e. rendimento cardiac e labor cardiac) sed plus tosto ab le puncto de vista del metabolismo intrinsec del myocardio, sin reguardo al character del manifestationes clinic o al externe travalio cardiac in le caso individual.

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Research is not something divorced from the ordinary activities of the wards or laboratory to be carried on in an exclusive way by some special group. It is a mode of working involving a mental attitude, a lively curiosity, an alertness in face of the unusual, an eagerness to utilize what fortune brings before one in the way of material for supplying gaps in our knowledge.—C. MACFIE CAMPBELL, M.D., late Professor of Psychiatry, Harvard University. *Annual Report of the Boston Psychopathic Hospital,* 1936, p. 11.

Congenital Familial Nodal Rhythm

By JAMES M. BACOS, Captain, U.S.A.F. (M.C.), JOHN T. EAGAN, M.D., AND EDWARD S. ORGAIN, M.D.

IT HAS BEEN KNOWN for years that the more serious cardiac arrhythmias, atrial fibrillation, atrial flutter,[1] and even ventricular tachycardia,[2] can exist in persons without demonstrable evidence of heart disease. One of the initial comprehensive reviews of this phenomenon was that of Orgain, Wolff, and White[1] in 1936, who reported 47 individuals presenting uncomplicated atrial fibrillation and 5 patients exhibiting atrial flutter.

The much rarer phenomenon of *familial* cardiac arrhythmias, to our knowledge, has been documented in the literature on only 4 occasions, and in each instance the arrhythmia was atrial fibrillation. Three normal brothers, who were included in the previous review,[1] were subsequently presented in a more extensive report by Wolff[3] in 1943. Additional case reports of atrial fibrillation in 2 elderly but apparently normal brothers were reported by Levy[4] in 1942. Lindqvist and Soderstrom,[5] in 1945, found uncomplicated atrial fibrillation in identical twins, 42 years of age. More recently, Gould[6] described a family covering 5 generations in which, of a total of 113 individuals, 10 men and 12 women were found to have atrial fibrillation without attendant abnormal cardiac findings. The earliest age of occurrence was 32 years. Four cases were described in detail, and in each instance this arrhythmia developed during or after the sixth decade of life. The fairly late onset of the arrhythmia in many of these individuals makes it difficult to eliminate completely the possibility of underlying arteriosclerotic heart disease as a predisposing factor.

A review of the pertinent literature has failed to disclose an example of a familial arrhythmic trait, specifically nodal bradycardia, so dominant as to express itself congenitally in all the offspring of a given ancestor. It is the purpose of this paper to report an example of such a familial trait. Recently, we have had the opportunity of examining 2 brothers who have manifested nodal bradycardia apparently since birth or early youth. Through them we have succeeded in obtaining histories and electrocardiograms of their parents, their siblings, and their offspring (fig. 1). Nine descendants exhibit nodal rhythm and probably have done so since birth. Of further interest is the development of paroxysmal atrial fibrillation in 4 individuals who have attained the fourth decade of life. We shall record and briefly discuss the case histories of 2 family members in detail.

Case Reports

Case 1

G. W. (fig. 1, IV-10) is a 50-year-old civil engineer who was referred to Duke Hospital for the management of a long-standing arrhythmia. During his childhood he was aware that his pulse was always slow, and although asymptomatic, he was restricted from engaging in strenuous athletics. In 1942 after being described as "100 per cent perfect with a pulse of 76 and a blood pressure of 130/80 mm. Hg," he was accepted for military service. During training, however, he noted transient episodes of "fluttering," weakness, and dyspnea. When examined for advancement to officer status, he was found to have a slow pulse and a heart murmur, and he was hospitalized with the tentative diagnosis of an interatrial septal defect. After refusing cardiac catheterization, he was given a medical discharge. Because of recurrent bouts of "fluttering" and shortness of breath, he found that he could no longer continue with the physically demanding job of civil engineering. He was then compelled to take a more sedentary position as a draftsman. While taking several medications in 1954, he developed an extensive dermatitis. All drug therapy was then withdrawn. From that time until 1958 he restricted himself to sedentary activities and apparently was

From the Department of Medicine, Duke University School of Medicine, and the Cardiovascular Service, Duke University Medical Center, Durham, N. C.

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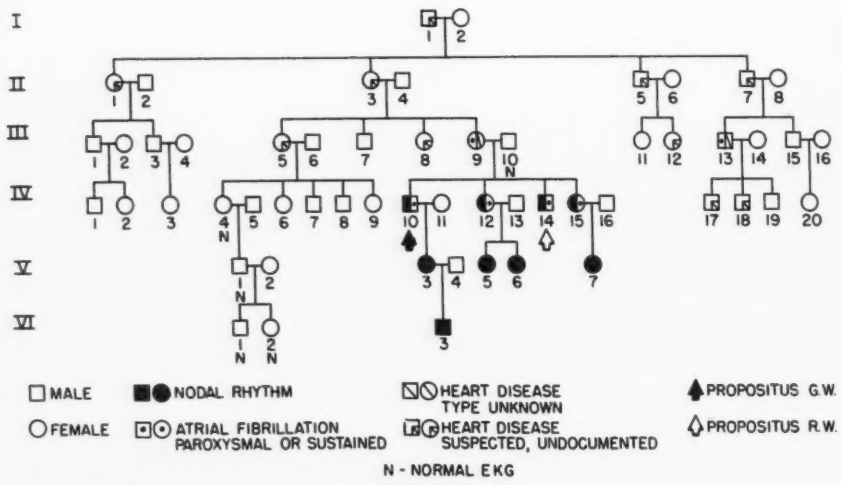

Figure 1

Genealogy of the maternal ancestor.

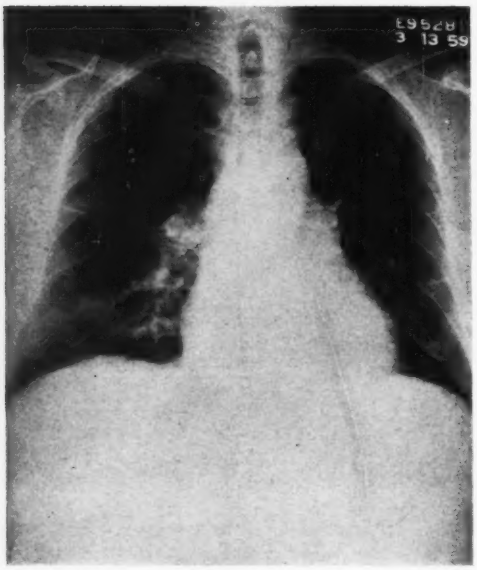

Figure 2

Chest x-ray and fluoroscopy on G.W., exhibiting large bilateral hilar shadows without associated pulsations. Moderate generalized cardiac enlargement is also present.

relatively asymptomatic. Late in 1958, however, he again developed sudden "fluttering," which required digitalis for control. One month prior to admission he experienced a sudden sensation that his "heart had stopped." This was followed by vague chest pain, shortness of breath, profuse perspiration, momentary loss of consciousness, and urinary incontinence. Shortly thereafter he was admitted to Duke Hospital. The patient's past history was otherwise unremarkable.

Physical examination revealed a moderately obese white man in no distress. Blood pressures were 130/90 mm. Hg supine and 140/90 mm. Hg standing. The radial pulse was grossly irregular at a rate of 84 beats per minute. There was no overt evidence of decompensation. The lungs were entirely clear. The heart on percussion appeared at the upper limits of normal in size. No thrills or shocks were noted. A grade-I systolic murmur was audible at the apex, and a systolic ejection sound was heard over the pulmonary out-flow tract. P_2 was greater than A_2 but was not split.

Laboratory studies revealed the following pertinent findings: multiple electrocardiographic tracings sent in by the patient's personal physician, covering a 10-year period from 1949 to 1959, recorded predominantly nodal bradycardia and on one occasion sinus bradycardia. Atrial fibrillation was observed in 1958. Subsequently a communication from another physician confirmed the presence of atrial fibrillation by electrocardiogram as early as 1945 and in 1947 nodal rhythm was recorded.

A baseline electrocardiogram on admission revealed atrial flutter-fibrillation with a ventricular rate of 80 and evidence of digitalis effect. Multiple chest x-rays and cardiac fluoroscopy disclosed "large hilar shadows, slight cardiac enlargement

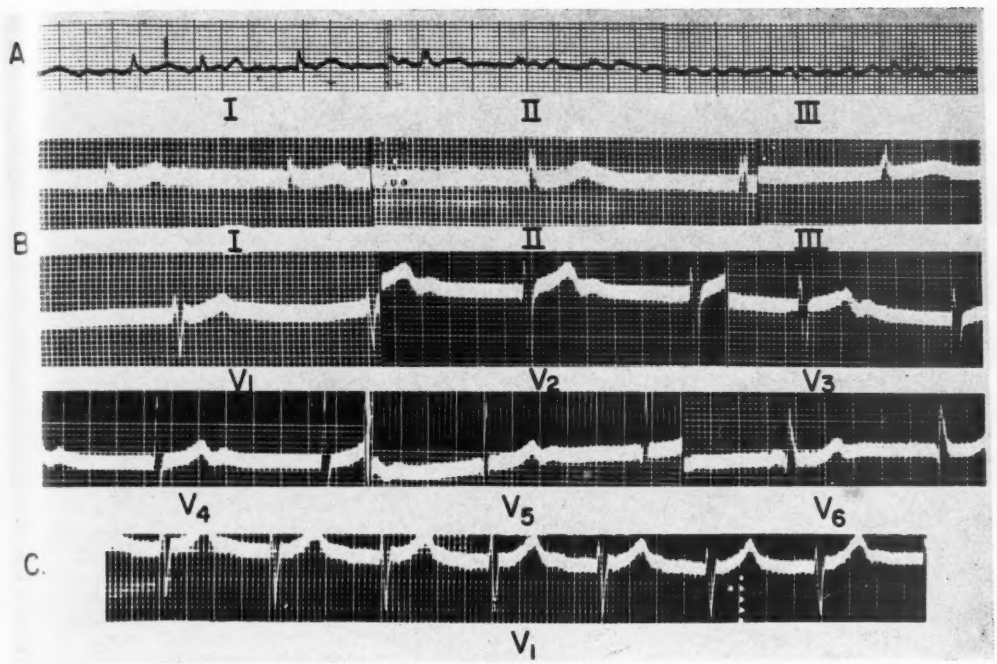

Figure 3

A. *Admission electrocardiogram on G.W. demonstrating atrial fibrillation.* B. *After conversion with quinidine, typical nodal bradycardia resulted.* C. *After 1.8 mg. of atropine the rate increased from 40 to 70 beats per minute.*

and a prominent pulmonary out-flow tract" (fig. 2).

Right heart catheterization and dye-dilution curves failed to reveal any evidence of intracardiac shunting. Right atrial and right ventricular pressures were normal. Pulmonary artery pressures were not obtained because of the development of ventricular irritability associated with mild chest pain and hypotension while the catheter was in the right ventricle. The procedure was therefore terminated and the patient quickly recovered without ill effects. Subsequently, under intense digitalis therapy his ventricular rate slowed to 60. Quinidine was then instituted and after 1.6 Gm. the rhythm reverted to a basic nodal bradycardia with an occasional wandering pacemaker and more rarely, isolated normal sinus beats. After exercise the ventricular rate increased by at least 10 beats above resting levels. Following intravenous atropine sulfate, 1.8 mg., the rate increased from a baseline of 45 beats per minute to a high of 75 beats per minute but nodal rhythm still persisted (fig. 3).

Because of the satisfactory response to atropine sulfate, the patient was discharged on 0.3 mg. of the drug 3 times a day. He returned 5 months later, having stopped the atropine sulfate because of distressing eye symptoms but having continued his quinidine, 0.4 Gm. 4 times a day. He continued to complain of easy fatigability and, on mild exertion, shortness of breath and "fluttering" of his heart. He had previously changed his occupation from draftsman to photographer but now found that he no longer had the energy to continue with either. His physical examination was essentially unchanged. The apical rate was 50 beats per minute and an electrocardiogram revealed wandering of the pacemaker from sinus to node. After 1.6 mg. of atropine intravenously, nodal rhythm appeared at a rate of 70. On the morning of the following day, after 15 mg. of dextro-amphetamine sulfate. in spansule form, he felt well and somewhat livelier than usual. A tracing showed nodal rhythm at a rate of 60 beats per minute. He was advised to continue dextro-amphetamine and quinidine therapy.

Case 2

R. W. (fig. 1, IV-14) a 42-year-old music teacher and brother of G. W., was admitted 1

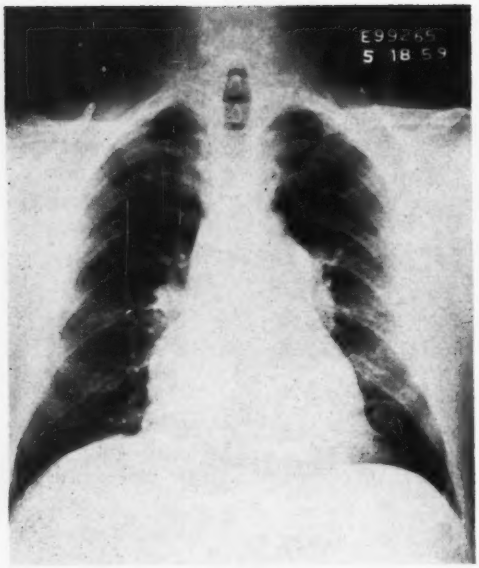

Figure 4

R.W. also exhibits slight generalized cardiomegaly with a markedly pulsatile pulmonary outflow tract.

month after his brother's discharge for evaluation of a similar cardiac arrhythmia. Their histories were quite similar. The patient enjoyed good health as a youth and participated in numerous sports, especially tennis. He was aware that his pulse was slow, usually about 50 beats a minute but he experienced normal growth and development without cardiovascular symptoms. At age 19 while in college he was denied life insurance because of an "enlarged heart and a heart murmur." On 3 occasions he was rejected from the service in World War II because of a "heart condition." His Selective Service record is quoted as stating "congenital malformed heart, rough systolic pulmonic murmur with thrill and increased pulmonary conus with relative stenosis." "X-rays showed widening of the upper part of the heart and hilar shadow, very likely cardiac enlargement." With the advent of war he left school and went to work in a powder plant, but when hostilities ceased he returned to college at the age of 30. It was here, while engaged in the strain of constant study, that he first experienced chest tightness and palpitation, which he described as a "nervous feeling." It was his impression that his first episode was gradual in onset and was unassociated with shortness of breath or ankle swelling. Symptoms gradually subsided over a 12-hour period during hospitalization. Subsequently numerous such episodes were experienced, oftimes in the wake of mental stress. Four years prior to admission quinidine prophylaxis was instituted, but he took the medication only sporadically. Despite these distressing episodes, he continued his activities as a band director and was apparently able to play wind instruments without difficulty. One month prior to admission, he developed an upper respiratory infection associated with fever, sweating, aching, and coughing. Then he developed a sudden episode of palpitation, which although controlled by digitalis, nevertheless persisted until his admission to Duke Hospital.

The general physical examination revealed a well-developed, moderately obese man in no distress. The supine blood pressure was 155/95 mm. Hg and standing 145/90 mm. Hg. The chest was symmetrical and expanded well. High-pitched squeaks and rhonchi were readily heard but no moist alveolar rales were heard. The heart was percussed approximately 11 cm. to the left of the midsternal line. No thrills or shocks were noted. The rhythm was grossly irregular with an apical rate of 120 beats per minute and a radial rate of 80 beats per minute. M_1 was split but no apical murmurs were heard. A systolic ejection sound was heard over the pulmonary out-flow tract; P_2 was greater than A_2 but was not split. The remainder of the examination was unremarkable and there were no signs of heart failure.

Baseline electrocardiograms revealed atrial fibrillation with a rapid ventricular response and numerous premature ventricular extrasystoles. Electrocardiograms accompanying the patient disclosed nodal rhythm in 1958. An electrocardiogram taken 2 months prior to admission exhibited atrial fibrillation with a ventricular response of 100 and occasional periods of ventricular tachycardia with multifocal extrasystoles. Multiple chest x-rays and fluoroscopy demonstrated the heart to be slightly enlarged in all diameters with a pulsating shadow along the left margin, suggesting an enlarged pulmonary out-flow tract (fig. 4). The secondary pulmonary branches did not pulsate actively. To the radiologist these findings suggested the presence of a possible patent ductus arteriosus.

During hospitalization digitalization was completed and then right heart catheterization was performed. The resulting oxygen samples and dye-dilution curves revealed no evidence of intracardiac shunting. All right-sided chamber pressures were normal and the cardiac output was 5 liters per minute at rest. Following catheterization quinidine administered orally in divided doses to a total of 2.4 Gm. reverted the rhythm to a basic nodal rhythm at a rate of 66, which subsequently slowed to 40 beats per minute. The cardiac rate increased with exercise but increased to a greater degree after atropine (fig. 5). Because of the

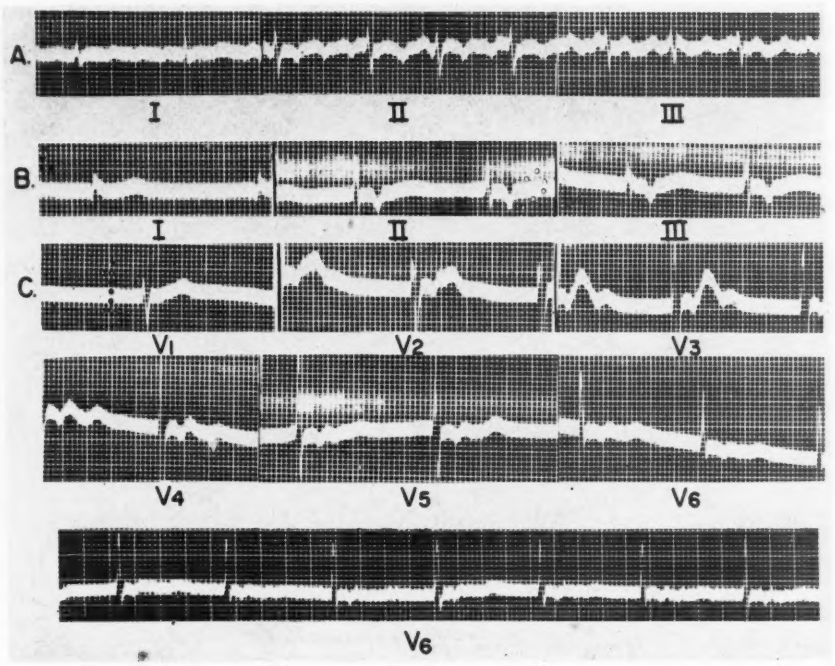

Figure 5

A. *Admission electrocardiogram on R.W., showing atrial fibrillation.* B. *After conversion with quinidine, nodal bradycardia resulted.* C. *After atropine, the rate increased to 70.*

relative lack of symptoms at this slow nodal rate the patient was discharged on maintenance quinidine therapy, 0.2 Gm. 4 times per day with a 0.2 Gm. enteric-coated tablet at bedtime.

On one return visit, he was found to have sinus bradycardia at a rate of 50 and on a second visit he had reverted back to nodal rhythm. He was given maintenance atropine but discontinued it because of disturbing side effects. At present his busy school schedule keeps him quite active and, accordingly, his rate during the height of the day is approximately 50 to 60 beats per minute, falling to 40 beats per minute late in the evening and upon arising. He is now taking quinidine 0.2 Gm. 4 times daily.

Discussion

In both brothers the presence of an arrhythmia and the striking x-ray findings of an enlarged pulmonary out-flow tract suggested either congenital heart disease or, less likely, pulmonary disease with secondary right heart enlargement. Though pulmonary function studies were not performed, there was no reason to incriminate pulmonary disease in G. W. and less reason in R. W. since, despite his mild chronic bronchitis, as a band director he plays wind instruments without difficulty. Other than nodal rhythm and atrial fibrillation the electrocardiograms in both patients show only minor T-wave changes. In R. W. cardiac catheterization revealed normal right-sided pressures, a normal cardiac output, and no increase in arteriovenous oxygen difference. In G. W. inability to traverse the pulmonary artery prevented us from obtaining samples for arteriovenous oxygen difference and Fick outputs; however, resting cardiac outputs performed by the dye-dilution method were normal. We therefore concluded that we could not incriminate any specific disease process to explain the radiologic findings.

Under normal circumstances, the cardiovascular system responds to peripheral demands with an increase in cardiac output

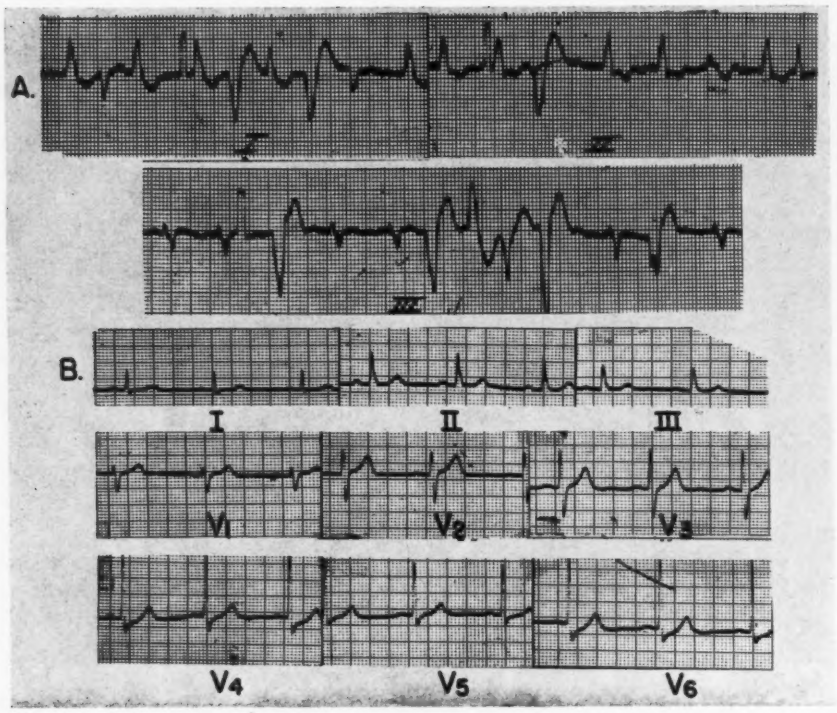

Figure 6

A. *Bipolar limb leads taken on the maternal ancestor 2 years prior to death. Atrial fibrillation with a rapid ventricular rate, left bundle-branch block, and multifocal premature contractions are present.* B. *In contrast this normal electrocardiogram was recently taken on the paternal ancestor who is still living and well at 72 years of age.*

primarily through an augmentation in both heart rate and stroke volume. It is suggested that in these individuals, just as in those with congenital heart block, nodal bradycardia significantly limits the tachycardiac response and therefore the increase in cardiac output can only be accomplished through an augmentation in stroke volume. Over a period of years the cardiovascular system may "physiologically adapt" to its limitations and this adaptation may manifest itself by cardiac enlargement.

The family history was striking. The patients' father (fig. 1, III-10) though elderly, enjoyed excellent health and was "healthier than the patient." The father has a normal electrocardiogram (fig. 6*B*) and is still living and well at 72 years of age without evidence of cardiac disease. The father's family is not included in figure 1 because they did not have any heart disease to the best of our knowledge: one sister age 80 is living and well; one brother age 70 is living and well; and one brother age 73 died of a cerebrovascular accident. Both of the father's parents are dead; the cause of their deaths is not known.

In contrast, many of the maternal family members are reputed to have or have had heart trouble. The mother of our patients (fig. 1, III-9) was informed of heart trouble after her marriage at 22 years of age, and was given only a short time to live. Contrary to prediction, she lived to the age of 71 years, working hard all her life. It is believed that in her early adult years she manifested a

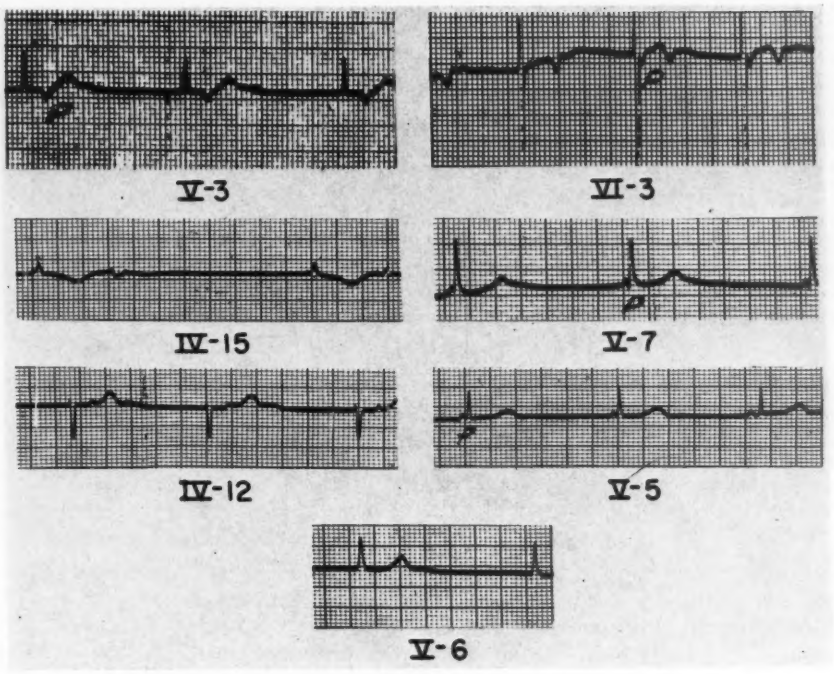

Figure 7

Representative leads from descendants with documented nodal rhythm. Roman numerals refer to the generation and arabic numerals refer to the individuals; refer to figure 1.

slow pulse, but during the last 20 years of her life she had documented atrial fibrillation. After years of borderline cardiac compensation she finally died in congestive heart failure. The electrocardiogram taken on the mother 2 years prior to death exhibited a markedly chaotic rhythm with atrial fibrillation and a rapid ventricular rate characterized by complete left bundle-branch block and numerous ectopic multifocal ventricular contractions, which simulate runs of ventricular tachycardia (fig. 6*A*). All 4 children (fig. 1, IV-10, 12, 14, 15) had nodal bradycardia, known to have been present as early as 9 years of age in one case, and all also developed documented paroxysms of atrial fibrillation. Characteristically this has occurred either late in the third decade or early in the fourth decade of life. Their respective offspring and even the grandchild of G. W. (fig. 1, VI-3), though asymptomatic, manifest a nodal rhythm, which seems to have occurred at birth (fig. 7). Table 1 illustrates in composite form certain characteristics of the arrhythmia as it applies to each member of the family.

Judging from the histories of our documented group, we can venture a prophecy that a very likely series of events occurring in subsequent members of this family might be as follows: a normal childhood and development without evidence of physical disability though characteristically the slow but regular pulse would be evident. Symptoms characterized by sudden transient episodes of a "fluttering or nervousness" in the chest may begin in the late twenties or early mid-thirties. Otherwise these individuals will be asymptomatic. Finally, there may occur established atrial fibrillation requiring definitive therapy for relief. Despite this discomforting picture, the total outlook does not appear distressing and the prognosis for

Table 1

Certain Characteristics of the Arrhythmia Tabulated for Each Family Member

Generation	III		IV				V				VI
Member	9	10	10	12	14	15	3	5	6	7	3
Age	Dead 71	72	50	41	42	46	30	5	12	20	14 mos.
Subjective estimate of health	—	good	poor	fair	fair	poor	good	good	good	good	good
History of "fluttering heart" or other suggestive cardiac symptoms	+++	—	+++	+	+	+++	—	—	—	—	—
Age of onset of "fluttering"	50	—	31	36	30	?	—	—	—	—	—
Known atrial fibrillation	+	—	+	+	+	+	—	—	—	—	—
Age slow heart rate first became apparent	—	—	early youth	9 years	late teens	early twenties	?	first year	first year	first year	first year
Documented nodal rhythm	—	—	+	+	+	+	+	+	+	+	+

longevity with proper precautions appears excellent.

The mechanism of this unusual familial characteristic remains highly conjectural. Genetically, it appears to be a dominant autosomal trait with an extremely high degree of penetrance. Initially, it was suspected that through an inherited defect there resulted congenital absence of the sinoatrial pacemaker, but the occasional occurrence of transient sinus bradycardia, seemingly emanating from the sinoatrial node even though infrequent, would tend to militate against this mechanism. Still another possible explanation could lie in the fact that the atrioventricular node and not the sinoatrial node is the dominant pacemaker, again through an inherited aberration. Why atrial fibrillation should subsequently occur in these individuals remains unknown. Recent experimentation by Scherf et al.[7] has shown that vagal stimulation under certain circumstances will consistently result in atrial fibrillation in the dog. Accordingly, one may entertain the possibility of nodal rhythm converting to atrial fibrillation in the presence of an inordinate degree of vagal tone. Whatever the exact mechanism is, this last point seems clear: like physical characteristics, unusual disturbances of cardiac rhythm may have a genetic mechanism of expression.

Summary

An unusual family group covering 3 generations is presented, all of whose members manifest a characteristic arrhythmia that appears to be an inherited trait. Each of the 9 known descendants exhibits a nodal bradycardia and each of the 4 descendants who have entered the fourth decade of life have also experienced paroxysms of atrial fibrillation. These paroxysms almost invariably terminate with the re-establishment of nodal rhythm. By history, the majority of these individuals are asymptomatic, and detailed examination of 2 adult members has failed to uncover evidence of specific cardiac disease. The problem of familial arrhythmia is briefly reviewed.

Summario in Interlingua

Es presentate un inusual gruppo familial con membros de 3 generationes qui omnes manifesta un arrhythmia characteristic que pare esser un tracto de hereditate. Omne le 9 cognoscite descendentes exhibi un bradycardia nodal e omne le 4 descendentes qui ha entrate in le quarte decennio de lor vitas ha etiam experientiate paroxysmos de fibrillation atrial. Iste paroxysmos se termina quasi invariabilemente in le restablimento de rhythmo nodal. In lor antecedentes le majoritate de iste subjectos es asymptomatic, e le detaliate examine de 2 membros adulte ha ...ro-

ducte nulle signo de specific morbo cardiac. Le problema de arrhythmia familial es revistate brevemente.

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Aneurism of the Aorta; Singular Pulsation of the Arteries, Necessity of the Employment of the Stethoscope

BY D. J. CORRIGAN, M.D.

Lecturer on the Institutes and Practice of Medicine; one of the Physicians of the Sick-Poor Institution, Dublin.

> "Such, however, was the power of prejudice, that it is observed, by Harvey, that no physician, passed the age of forty, believed in his doctrine; and that his practice declined from the moment he published this ever-memorable discovery." *Medical Facts,* Vol. 1.

Many of the profession still view with scepticism the utility of the stethoscope, in ascertaining the exact nature of thoracic disease.

I shall not enter into any general discussion on the merits of the instrument. This is obvious, that those who use it have not only all the information to be derived from symptoms, history of the disease, etc., which its opponents enjoy; but that, in the instrument, they have a medium super-added through which to obtain additional knowledge, and they are thus enabled to come to the examination of thoracic disease, as it were, with increased powers of mind.—*The Lancet,* 1:586, 1829.

Observations on the Occurrence of Right Bundle-Branch Block Following Open Repair of Ventricular Septal Defects

By J. David Bristow, M.D., Donald G. Kassebaum, M.D., Albert Starr, M.D., and Herbert E. Griswold, M.D.

THE DEVELOPMENT of conduction disturbances attending the direct closure of ventricular septal defects might be anticiapated in view of the promixity of the ventricular conduction system. Early reports of open intracardiac operations described the appearance of complete heart block in a number of patients undergoing surgery on the ventricular septum.[1, 2] Recent studies have suggested the more frequent occurrence of right bundle-branch block concomitant with this operation.[3, 4]

The intent of the present study was to determine the occurrence of right bundle-branch block in a group of patients who underwent corrective open-heart surgery, and to correlate the development of the conduction abnormality with the location of the ventricular septal defect. The possible influence of right ventriculotomy alone on the delayed depolarization process was also considered.

Material and Methods

On each of the 27 patients studied, corrective intracardiac surgery was performed at the University of Oregon Medical School Hospitals, utilizing total cardiopulmonary bypass with a mechanical pump-oxygenator. Twenty-five of these patients represented a consecutive group of survivors of surgery for ventricular septal defect. Ten of these had associated congenital cardiac anomalies. The ventricular defects were closed by silk sutures or with Ivalon patches. Additional procedures included the closure of a coexisting atrial septal defect, pulmonary valvotomy, infundibular resection, and Teflon roof-expansion of the right ventricular outflow tract. Patients were excluded from the study who died during surgery or in the postoperative period before complete electrocardiographic study was feasible. Patients with complete heart block were also excluded.

The cases were classified on the basis of the surgical approach. Group I consisted of 21 patients whose septal defects were closed through a right ventriculotomy. In the 4 cases included in Group II, the defects were repaired through a right atriotomy. Group III consisted of 2 patients who had right ventriculotomy but did not have ventricular septal defects.

The ventricular septal defects were classified according to their location (fig. 1): (1) true outflow defects located superior to the crista supraventricularis and inferior to the pulmonary valve; (2) anterior septal defects, inferior to the crista supraventricularis and not extending posteriorly to the tricuspid ring or involving a major part of the membranous septum; (3) defects in the membranous septum and juxtaposed to the tricuspid ring; and (4) defects in the posterior muscular septum that were hidden beneath the septal or the posterior leaflet of the tricuspid valve. In a number of cases, the defect involved two of the areas.

Preoperative and postoperative electrocardiograms were analyzed for the QRS pattern and duration and the time of the onset of the intrinsicoid deflection in the right precordial leads.

Results

The preoperative electrocardiograms were normal in some cases, but the majority showed evidence of right ventricular hypertrophy or incomplete right bundle-branch block, based on the Wilson criteria.[5] None of the preoperative electrocardiograms displayed complete bundle-branch block. Changes in ventricular conduction were considered significant if the QRS duration increased at least 0.02 second. Such prolongation of conduction was uniformly associated with definite changes in the QRS configuration (table 1).

Group 1 (A), 13 Patients

Of the 21 cases in group I, 13 displayed an increase in QRS duration postoperatively. The mean QRS duration in these was 0.08 second preoperatively and 0.11 second postoperatively. In those with slight changes in QRS duration (0.02 second) there were alterations in the QRS configuration and delayed

From the Division of Cardiology, Department of Medicine, the Division of Thoracic Surgery, Department of Surgery, and the Crippled Children's Division, University of Oregon Medical School, Portland, Ore.

onset of the intrinsicoid deflection in lead V_1. The mean duration of the latter was 0.05 second before, and 0.08 second after surgery. Individual cases increased as much as 0.06 second. Eight patients had complete right bundle-branch block postoperatively with QRS durations of 0.12 second or longer.

The ventricular septal defects in 12 of these cases involved areas 2, 3, or both, and were repaired through a right ventriculotomy. In 7 of these, both areas were involved by defects at least 2 cm. in diameter. In only 1 patient was the septal defect located above the crista supraventricularis. None of this group had lesions of the posterior muscular septum.

Group I (B), 8 Patients

Significantly increased QRS duration after transventricular surgery was not seen in these members of the first group. The mean QRS duration of 0.08 second was unaltered by surgery.

Three of these defects were in the outflow tract above the crista supraventricularis. One posterior muscular septal defect was encountered. The remaining 4 were in areas 2 and 3

Group II, 4 Patients

In these cases, the defects lay in areas 3 and 4, and were repaired through a right atriotomy,[6] thereby precluding ventriculotomy. Significant increase in QRS duration after surgery was not seen.

Group III, 2 Patients

Neither of these cases was found to have a ventricular septal defect after inspection of the septum through a right ventriculotomy. Both showed alterations in the QRS configuration postoperatively, but the QRS duration did not change.

Discussion

The anatomic relationship of the ventricular conduction system to ventricular septal defects became an important consideration when complete heart block was seen to follow their repair. Of additional interest, was the appearance of varying degrees of right bundle branch block postoperatively.

Discussions by Lillehei and Kirklin of a paper by Kirklin et al.,[2] presented observations on the development of complete heart block when a suture was placed through the posteroinferior rim of certain septal defects. Their conclusions concerning the vulnerability of the inferior angle of these defects of the membranous ventricular septum were quite accurate in view of the later detailed anatomic studies by Truex and Bishof.[7] They demonstrated the fairly constant relationship of the common bundle of His to the posterior margin of such defects. The right bundle-branch was variable in size and location, but often reached a subendocardial position in the inferior margin of the ventricular septal

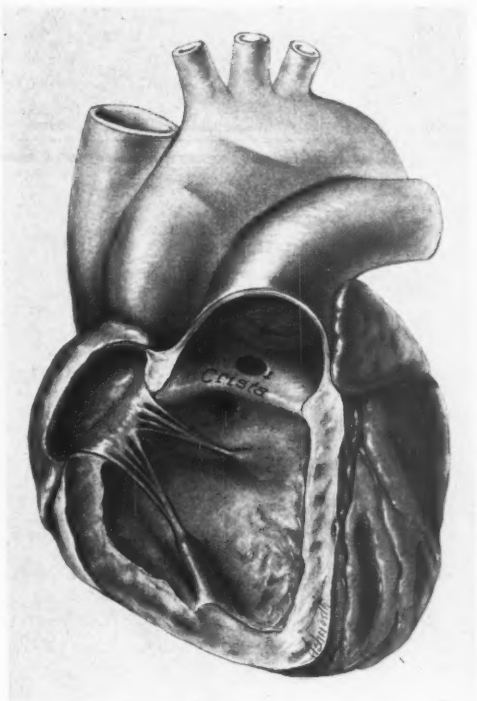

Figure 1

Schematic drawing of the right ventricular aspect of the interventricular septum, depicting the locations of ventricular septal defects in the present series. 1, true outflow defect; 2, anterior septal defect, inferior to the crista supraventricularis; 3, membranous septal defect, juxtaposed to the tricuspid ring; 4, defect in the posterior muscular septum. The interrupted line includes the two areas commonly involved by a single defect.

Table 1

Electrocardiographic and Clinical Data in Twenty-Seven Patients

Case	Age	Diagnosis	Preoperative ECG QRS form	Preoperative ECG QRS duration (sec.)	Preoperative ECG Intrin. V_{-1}	Postoperative ECG QRS form	Postoperative ECG QRS duration (sec.)	Postoperative ECG Intrin. V_{-1}	Area of defect	Size of defect (cm.)
Group I (subgroup A), ventriculotomy and closure VSD with change in QRS duration.										
D.V.	9	VSD	QR	0.08	0.03	rsR′	0.13	0.09	2	1
J.L.	2	VSD	rSR′	0.08	0.04	rsR′	0.12	0.09	2, 3	2
D.S.	16	VSD-IS	rsR′	0.11	0.08	rsR′	0.13	0.09	1, 2	3
J.W.	7	VSD	Rsr′	0.07	0.06	rR′	0.12	0.09	2, 3	2
W.G.	3	Tetralogy	Rs	0.07	0.04	rsR′	0.12	0.08	2, 3	2½
W.S.	12	VSD-IS	rSr′	0.07	0.04	rsR′	0.12	0.09	1	1
M.B.	3	VSD	RSR′	0.08	0.05	rsR′	0.10	0.08	3	1
C.A.	4	Pentalogy	rS	0.05	0.02	rSR′	0.09	0.07	2, 3	2
S.Y.	3	VSD	rsR′s′	0.06	0.05	rsR′	0.10	0.08	2, 3	2½
L.L.	3	VSD	rSr′	0.06	0.05	rSR′	0.08	0.07	2	1½
H.L.	4	ASD-VSD	rSR′	0.07	0.06	rSR′	0.11	0.08	3	2
T.C.	8	VSD	rsR′	0.10	0.08	rsR′	0.12	0.09	2, 3	2
B.G.	18	Tetralogy	R	0.09	0.05	rsR′	0.12	0.09	2, 3	2
Group I (subgroup B), ventriculotomy and closure VSD without change in QRS duration.										
G.S.	10	Tetralogy	qR	0.07	0.04	qR	0.07	0.03	2, 3	3
C.H.	12	VSD	rS	0.08	0.02	rS	0.08	0.02	2	1¼
D.G.	5	VSD	RS	0.08	0.02	RSr′s′	0.08	0.04	2	1½
C.B.	21	VSD-ASV	rS	0.09	0.02	rS	0.09	0.02	1	1¼
M.V.	6	VSD	rS	0.07	0.02	rSr′	0.08	0.01	1	2
T.S.	7	VSD	rsR′s′	0.08	0.05	rSR′	0.08	0.06	4	½
C.W.	6	VSD	rsr′	0.08	0.02	rS	0.08	0.02	1	½
G.M.	6	VSD	RS	0.10	0.03	rsR′	0.09	0.09	2, 3	1½
Group II, atriotomy and closure VSD										
G.A.	14	VSD-CT	rS	0.07	0.01	rSr′	0.08	0.05	3, 4	1½
M.L.	20	IAVC-VSD	rsR′	0.11	0.08	rSR′	0.10	0.07	4	2
N.E.	6	VSD	RS	0.07	0.04	rSR′	0.08	0.04	3	1
J.R.	10	VSD	rS	0.08	0.02	rS	0.07	0.02	3	1
Group III, ventriculotomy and septal exploration. VSD not present.										
T.J.	7	PDA-PH	Rs	0.07	0.02	QR	0.08	0.05		
N.B.	10	PS-PFO	qR	0.08	0.04	qr	0.08	0.05		

Key to abbreviations: VSD, ventricular septal defect; IS, infundibular stenosis; ASD, atrial septal defect; ASV, aneurysm of the sinus of Valsalva with rupture into the right ventricle; CT, cleft tricuspid valve; IAVC-VSD, incomplete atrioventricularis communis with ventricular septal defect; PDA-PH, patent ductus arteriosus with pulmonary hypertension; PS-PFO, pulmonic stenosis with patent foramen ovale.

defects. Occasionally, both right and left bundle-branches descended anterior to the defects. Sutures placed in the posterior or inferior margins of a defect could, therefore, traumatize conduction tissue directly, or result in injury because of edema or microhemorrhage. The right bundle-branch would be especially vulnerable to trauma because of its subendocardial position. The occurrence of persistent right bundle-branch block following pulmonary valvotomy or infundibular resection[8] has been explained on this basis.

The majority of ventricular septal defects in this study were in areas 2 or 3, in juxtaposition to the ventricular conduction tissue. All but 1 of the 13 cases that showed significantly altered conduction had defects involving these areas, and among these, 8 developed complete right bundle-branch block. The only exception in this group had infundibular resection in addition to closure of his septal defect. In some cases, however, repair of defects in this location did not result in conduction disturbances postoperatively. For ui-

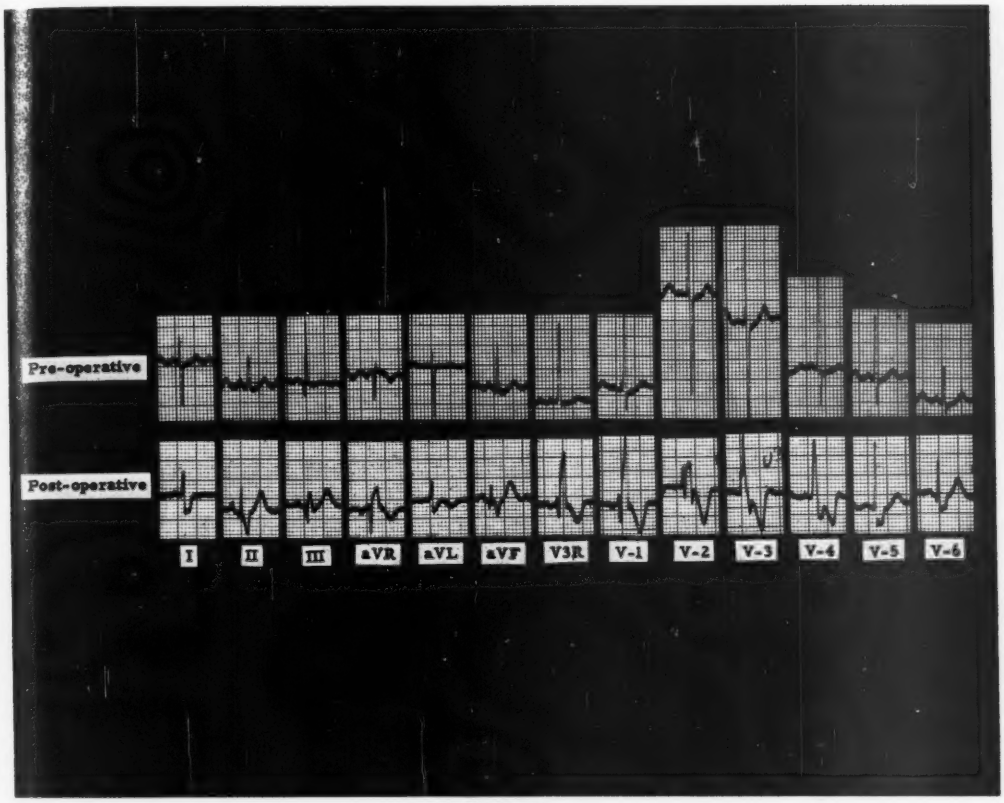

Figure 2

Patient W. G. Tetralogy of Fallot. Following total surgical correction, the form of the electrocardiogram was altered from typical right ventricular hypertrophy to right bundle-branch block.

tous placement of sutures and the anatomic variability of the conduction pathways might account for this.

The posterior position of the defects in areas 3 and 4, unrelated to the ventricular conduction system, precluded the development of disturbed conduction and made repair possible through an atriotomy.

In 6 patients, pulmonary stenosis was associated with the ventricular septal defect. Five of these developed QRS prolongation after surgery and in 4 the defect was in areas 2 or 3. In our experience, ventricular septal defects with pulmonary stenosis have been found most often in areas 2 and 3 and thus repair could reasonably lead to the development of right bundle-branch block.

It might be postulated that ventriculotomy alone may result in some degree of intraventricular conduction delay. In the 2 cases in which ventriculotomy without septal surgery was done, significant QRS prolongation did not occur postoperatively, but in both instances the QRS configuration was changed. Only minor conduction abnormalities should result from the ventricular incision, which does not involve major conduction pathways.

Summary

The occurrence of right bundle-branch block and varying degrees of altered ventricular conduction in a group of cases of ventricular septal defects repaired by direct closure is presented.

The development of abnormal conduction

is correlated with the location of the ventricular septal defects and the relationship of the conduction tissue.

The etiologic role of operative trauma to the conduction system is reviewed, and the influence of ventriculotomy alone is discounted.

Summario in Interlingua

Es reportate le occurrentia de bloco de branca dextere con varie grados de alteration del conduction ventricular in un gruppo de casos de defecto ventriculo-septal reparate per clausion directe.

Le disveloppamento de conduction anormal es correlationate con le sito del defectos ventriculo-septal e le relation del tissu de conduction.

Le rolo etiologic de trauma operatori con respecto al systema de conduction es revistate. Es rejicite le responsabilitate de ventriculotomia per se.

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Man a Microcosm

For first we are a rude mass, and in the rank of creatures which only are, and have a dull kind of being, not yet privileged with life, or preferred to sense or reason; next we live the life of Plants, the life of Animals, the life of Men, and at last the life of Spirits, running on in one mysterious nature those five kinds of existences, which comprehend the creatures, not onely of the World, but of the Universe.—Sir Thomas Browne. *Religio Medici.* Edited by W. A. Greenhill, M.D. London, Macmillan and Co., Ltd., 1950, p. 56.

The Effect of Lipemia upon Tissue Oxygen Tension in Man

By Claude R. Joyner, Jr., M.D., Orville Horwitz, M.D., and Phyllis G. Williams, B.S.

SUBSEQUENT to the observation that the intravenous infusion of fat emulsion caused a decrease in the myocardial oxygen tension of dogs having an experimentally produced myocardial infarction, it was shown that the hyperlipemia following a large fat meal may precipitate an attack of angina pectoris in patients with severe coronary artery disease.[1-3] These attacks of angina developed about 5 hours after the fat meal, when lipemia was near its peak. Although sublingual nitroglycerin gave subjective relief, the lipemia-induced angina could also be relieved by the intravenous injection of heparin. The plasma turbidity and triglyceride level decreased following heparin, as expected, due to lipoprotein lipase activity.[4-8] Therefore, it appeared that the level of lipemia had an effect upon the myocardium, i.e., anginal attacks developed at the time of hyperlipemia and were relieved by heparin, which induced "clearing" of plasma. Since increasing the blood fat level in the dog decreased myocardial oxygen tension, the present study was undertaken in order to determine whether the level of lipemia affects tissue oxygen tension in man.

The polarographic method of oxygen tension determination, which was used in the study of the dog myocardium during fat infusion, is also a useful tool for investigation of oxygen tension in accessible tissue of man. It has been particularly adaptable to determinations of skin oxygen tension, and thus used extensively in the study of peripheral vascular disease. The limitations of the polarographic method, and the considerable information that has been obtained by its use, have been well summarized by Montgomery.[9]

In preliminary experiments we had attempted to measure oxygen tension of the skin as lipemia developed following a fat meal. As might be expected, valid determinations of oxygen tension over the several hours of increasing lipemia after fat ingestion were difficult to make. The polarographic method is most accurate when the subjects remain quiet, the electrode position is not disturbed, and the experiment is brief enough so that the slight downward "drift" of readings which always occurs when electrodes are in place for long periods will not hamper interpretation of data. The following procedure was therefore adopted in which oxygen tension determinations were made over reasonably brief periods during which plasma turbidity either remained at a constant level or decreased after heparin administration.

Method

Twelve subjects, ranging in age from 33 to 77 years, were studied. The serum levels of cholesterol, total esterified fatty acid, and phospholipid were normal in the fasting state in all patients; although several had clinically evident peripheral arteriosclerosis. Six subjects (A.N., T.S., A.P., G.T., M.S., J.G.) had no palpable pulses in the feet and poor skin blood flow as measured by the vasodilatation test; 3 subjects (A.C., M.G., and V.R.) had claudication of one extremity but no objective evidence of decreased blood flow to the feet; and 3 subjects (C.A., E.D., and J.K.) had neither symptoms nor signs of peripheral vascular disease. The basic design of the experiment was as follows.

Subjects had not smoked and had taken nothing by mouth except water for 16 hours before each study period. Lipemia was induced by a fat meal containing 0.6 Gm. of butterfat per pound of body weight. Following this meal, consisting of heavy cream flavored with cocoa and cyclamate, subjects were permitted only water by mouth and did not smoke until the study was completed. They

From the Edward B. Robinette Foundation, Medical Clinics, Hospital of the University of Pennsylvania, Philadelphia, Pa.

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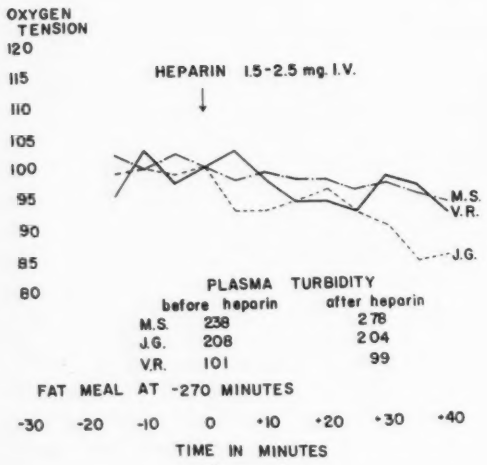

Figure 1

Cutaneous oxygen tension and plasma turbidity of 3 subjects given 1.5 to 2.5 mg. of heparin 4½ hours after a fat meal.

remained at rest, sitting or lying down as desired, until measurements of skin temperature and oxygen tension were begun 4 to 4½ hours after the fat meal. Studies were made with subjects reclining in a room with air temperature of 23 ± 1 C., which did not vary more than ±0.5 C. during any one study period. Skin temperature of the toes was recorded from thermocouples. Four platinum electrodes were inserted intradermally at the base of the toes for determination of cutaneous oxygen tension by the polarographic technic in use in this laboratory.[10] Per cent changes in oxygen tension were calculated from the direct galvanometric readings obtained from the 4 electrodes. After a 20- to 30-minute control period of stable skin temperature and oxygen tension had been obtained, a sample of venous blood was drawn and an injection of heparin given through the same needle. Determinations of skin temperature and oxygen tension were continued at 5-minute intervals over the subsequent 40 minutes, at which time another venous blood sample was obtained. This terminated the study period.

The dose of heparin given 4½ to 5 hours after the fat meal was 1.5 to 2.5 mg. in 3 subjects (V.R., M.S., and J.G.). In all other studies using heparin a dose of 15 to 20 mg. was injected.

For the plasma turbidity study 8.5 ml. of venous blood were mixed with 0.5 ml. of M/10 sodium oxalate and immediately centrifuged for 10 minutes at 3,000 R.P.M. Readings of plasma against a water blank were obtained with a Klett-Summerson photoelectric colorimeter with a red (640-700mμ) filter.

To compare the oxygen tension during fairly stable levels of hyperlipemia with that observed during heparin-induced plasma clearing, 5 of the subjects who received a 15 to 20 mg. injection of heparin were studied on another day when the identical experiment was repeated, except that 1 ml. of saline was given instead of heparin. One additional subject (G.T.) was studied with saline injection but was unavailable for a comparative experiment with heparin.

To determine whether cutaneous oxygen tension is affected by heparin injection when the plasma is "clear," 4 of the subjects in whom studies had been made with heparin and saline injections during postprandial lipemia were studied on another day when the plasma turbidity was low subsequent to a 16-hour fast. A blood sample was obtained after the standard control period; 20 mg. of heparin were injected intravenously, and the usual measurements were made over the subsequent 40 minutes.

Results

The plasma turbidity and cutaneous oxygen tension of the 3 subjects given less than 3 mg. of heparin 4½ hours after the standard fat meal are summarized in figure 1. M.S. and J. G. received 1.5 mg. of heparin; V.R. received 2.5 mg. A downward "drift" in oxygen tension was found in all 3 subjects; the plasma turbidity 40 minutes after heparin was not significantly decreased from the preheparin value in any patient. The trend of the oxygen tension in V.R. was similar to that of the 2 other patients, although this 57-year-old woman had diarrhea the day of the test and her plasma turbidity did not reach the level usually attained. In all 3 subjects, the skin temperature remained stable during the course of the experiment. The presence of severe peripheral arterial disease did not appear to affect the results. M.S. and J.G. had absent foot pulses and poor skin flow, as measured by the vasodilatation test. V.R. complained of claudication of one calf, but had a normal response to vasodilatation and excellent pulses in the feet.

The findings in all other experiments are summarized in table 1. A gradual increase in oxygen tension was recorded during the 40 minutes following heparin injection in all 8 subjects given 15 to 20 mg. of heparin 4½ to 5 hours after a fat meal. The increase in

Table 1

Changes in Oxygen Tension and Plasma Turbidity over Forty-Minute Period Following Heparin or Saline Injection

Subject	Heparin 4 1/2 to 5 hr. after fat meal		Saline 4 1/2 to 5 hr. after fat meal		Heparin fasting	
	Change O_2 tension	Change in turbidity	Change O_2 tension	Change in turbidity	Change O_2 tension	Change in turbidity
A. N.	+56	−160 (51)	−31	− 5 (2)	−10	−11 (14)
C. A.	+36	−149 (38)	− 1	+ 5 (2)	− 9	+ 4 (11)
E. D.	+23	− 70 (29)	− 7	− 7 (3)		
T. S.	+22	−118 (68)	−10	+10 (5)	− 7	− 1 (2)
A. C.	+12	− 91 (32)	− 1	+ 2 (0)	−12	− 3 (5)
J. K.	+13	− 50 (45)				
A. P.	+ 8	− 89 (51)				
M. G.	+ 4	−110 (41)				
G. T.			0	−10 (5)		

Oxygen tension expressed as per cent change from control level at time of injection. Turbidity expressed as change from control level in Klett units and per cent change in parentheses. Minus (−) change in turbidity reflects clearing of plasma and plus (+) an increase in turbidity.

cutaneous oxygen tension ranged from 4 to 56 per cent, with a mean of 21.7 per cent. As expected, plasma turbidity was appreciably decreased following the injection of this dose of heparin.

It was not possible, however, to establish a direct relationship between the magnitude of change in oxygen tension and the per cent of clearing of plasma or absolute decrease in plasma turbidity. For example, A.N. and A.P. each showed a 51 per cent decrease in turbidity; but A.N. had an increase in oxygen tension of 56 per cent in contrast to the 8 per cent increase of A.P. The greatest decrease in absolute turbidity was shown by the 2 subjects (A.N. and C.A.) having the greatest increase in oxygen tension. However, the 2 subjects (A.P. and M.G.) having the least increase in oxygen tension showed a decrease in turbidity similar to that of E.D. and T.S., who each had a more than 20 per cent increase in oxygen availability. Also, there was no correlation between oxygen tension change and the level of plasma turbidity at the time of heparin injection. The plasma turbidity (Klett units) at the time of heparin injection in 3 subjects representing greatest oxygen tension change, near mean change, and least change was: A.N. –310, T.S. –175, and M.G. –70.

The change in oxygen tension did not appear to be influenced by the presence or absence of peripheral artery disease. As noted above, A.N., T.S., A.P., G.T., M.S., and J.G. had no palpable pulses in the feet and very poor skin flow by the vasodilatation test. The other 6 subjects had no objective evidence of impaired peripheral blood flow.

There was no significant change in the skin temperature of the toes in any of the subjects.

In contrast to the effects observed after the injection of 15 to 20 mg. of heparin, there was no increase in cutaneous oxygen tension when 1 ml. of saline was injected 4½ to 5 hours after a fat meal. As noted in table 1, a slight, insignificant increase or decrease in plasma turbidity was found 40 minutes after the placebo injection. Figure 2 presents a comparison of the effects of saline and heparin injections in all studies performed after a fat meal. The mean turbidity before injection was somewhat lower in the saline experiments than in the heparin series due to subject G.T. having a low postprandial lipemia curve with a peak of 150 units and E.D. having a lower turbidity reading on the day of saline than on the day of heparin injection.

The results of the 2 studies in subject E.D. are shown in figure 3. It should be emphasized that the oxygen tension determinations in this

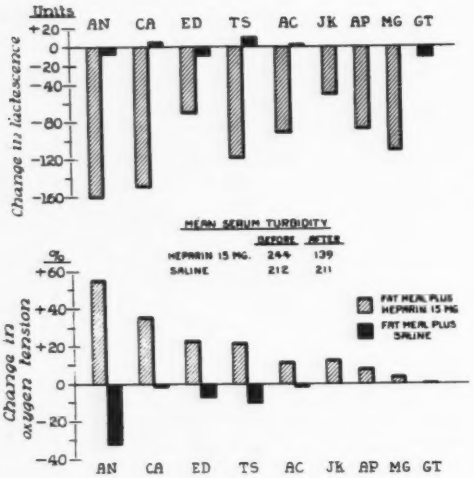

Figure 2

Changes in lactescence and oxygen tension over the 40-minute period following injection of 15 mg. of heparin; and following saline injection 4½ to 5 hours after a fat meal.

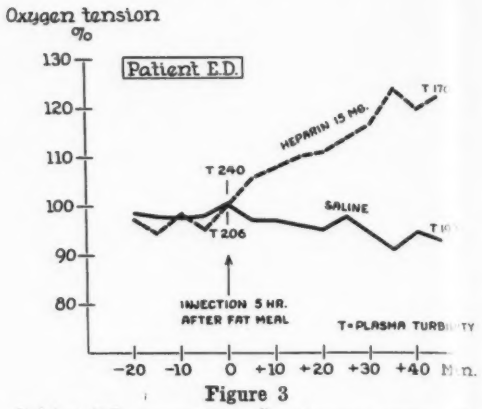

Figure 3

Subject E.D. comparison of cutaneous oxygen tension and plasma turbidity after injection of 15 mg. of heparin and after saline injection 5 hours following fat meal.

study were done with uncalibrated electrodes, since calibration of these electrodes in human skin is subject to a 25 per cent error.[10] Therefore, studies obtained on different days with different electrode placement should not be considered to reflect absolute oxygen tension on the different days. The technic is ideally suited for the measurement of *changes* in oxygen tension over brief periods, as was seen following heparin injection in E.D. and the other subjects. Each study should be considered against its own control period. For example, the absolute cutaneous oxygen tension during the entire saline study in E.D. may have been higher than the absolute level 40 minutes after heparin. What should be emphasized is that there was an increase from the control level following heparin injection and no increase after saline injection.

Another representative response to heparin injection following a fat meal is shown in figure 4, which summarized 3 of the 4 studies in patient T.S. The increase in tissue oxygen tension following heparin injection and the lack of increase following saline injection is similar to the response of patient E.D. and the other subjects. In addition, the consistency of the postprandial lipemia curves in patient T.S. made it possible to obtain measurements of oxygen tension during his spontaneous clearing of lipemia. The increase in oxygen tension during the first hour of spontaneous clearing from the peak of lipemia is plotted on the right in figure 4. Therefore, an increase in oxygen tension was found during spontaneous clearing as well as during heparin-induced decrease in lipemia.

As a fourth study in this patient, he received 20 mg. of heparin intravenously after a 16-hour fast. The results obtained in T.S. and the 3 other subjects given 20 mg. of heparin when the plasma turbidity was low due to a 16-hour fast are charted in figure 5. The injection of heparin in subjects having low-plasma turbidity due to fasting did not result in the increase in oxygen tension seen following the injection of heparin when there was significant gross lipemia. An increase in oxygen tension was found only in those situations in which there was clearing of gross lipemia.

Discussion

From these studies, it would appear that tissue oxygen tension in man is affected by the level of lipemia. The cutaneous oxygen tension of the toes increased coincident with heparin-induced clearing of plasma turbidity.

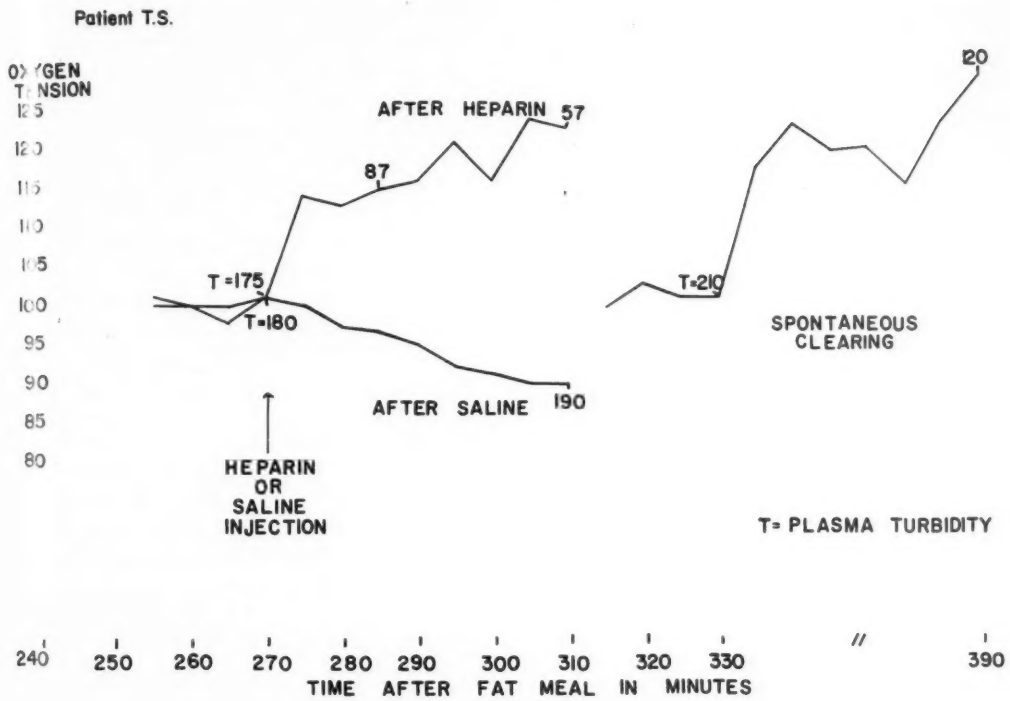

Figure 4

Subject T.S. cutaneous oxygen tension and plasma turbidity after saline injection and after heparin injection 4½ hours after a fat meal. Curve to the right is response noted during 1 hour of spontaneous clearing from peak of postprandial lipemia.

In 1 subject a similar increase of oxygen tension was demonstrated during the spontaneous decline of postprandial lipemia.

This increase in skin oxygen tension that occurred during heparin clearing is appreciable, exceeding that produced in normal and ischemic limbs by change from the horizontal position to dependency for 20 minutes.[11] The changes in tissue oxygen do not appear to have been due to the administration of heparin per se, since injections given to fasting subjects had no demonstrable effect.

The measurements obtained with the intracutaneous electrodes used in this study are believed to reflect oxygen tension of tissue rather than of blood. The delivery of oxygen to the tip of an electrode inserted into skin is dependent upon several potentially variable factors. These are (1) flow of blood to the skin, (2) oxygenation of the blood, and (3) diffusion of oxygen from the erythrocytes to the electrode. It is quite unlikely, although possible, that the changes in tissue oxygen tension that occurred during plasma clearing resulted from changes in cutaneous blood flow. The presence or absence of apparent peripheral artery disease, and the response of the subjects to the vasodilatation test, could not be correlated with the oxygen changes noted during plasma clearing. For example, subject T.S. (fig. 4) had very ischemic feet. The vasodilatation test showed no evident capacity for increase in cutaneous flow when our studies were performed. He later had a sympathectomy and the vasodilatation test was repeated following the intravenous injection of Priscoline. Again, no capacity for increase in cutaneous flow could be detected.

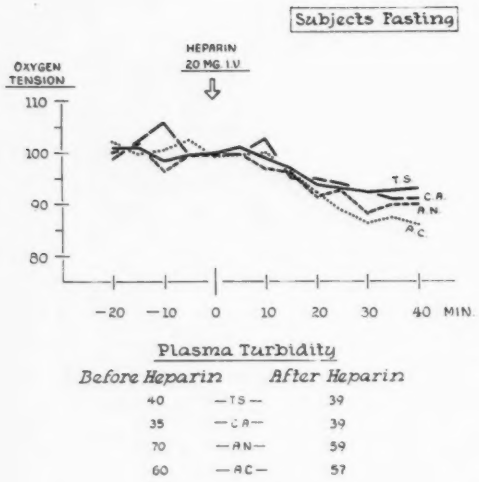

Figure 5

Cutaneous oxygen tension and plasma turbidity of subjects given 20 mg. of heparin intravenously after a 16-hour fast.

Also, all of our subjects had stable skin temperature readings during the course of the experiments. Minor changes in flow may occur without changes in skin temperature. However, the skin temperature has been found to bear a good relationship to the blood flow determined by plethysmography when room temperature is the same (23 ± 1 C.) as that employed in our studies.[12]

If, as seems likely, the level of lipemia does affect oxygen diffusion, it may well influence oxygen uptake in the lungs as well as release to the other tissues. We had previously noted an unusual increase in rate and depth of respiration which seemed characteristic of lipemia-induced angina pectoris.[1, 2] In 2 subjects with hyperlipemia and congestive failure, arterial oxygen saturation apparently increased when the serum triglyceride level was decreased by several weeks of strict diet.[13] The coexisting congestive failure in these 2 patients may have made detectable an impairment of blood oxygenation not demonstrable in hyperlipemic subjects with normal heart and lungs. Several years ago Martin and Hueper reported a decreased rate of oxygen uptake by the erythrocytes of hypercholesteremic rabbits.[14] Coating of the red blood cells or streaming of chylomicrons might hinder the diffusion of oxygen between erythrocytes and tissues. Other effects of lipemia have been reported which might hinder diffusion. Increased adhesiveness and aggregation of red blood cells have been observed.[15] Lipemia may affect blood viscosity. An increase in viscosity has been reported during lipemia, but another study failed to demonstrate an increase in viscosity during lipemia or a decrease in viscosity after heparin injection.[15, 16] Sludging of blood may be important, particularly in smaller vessels.[3, 17] Any of these factors, or others, may be responsible for the observed effect of varying levels of lipemia upon tissue oxygen tension.

The results of the present study indicate that the oxygen tension of at least one tissue in man—the skin—is affected by the level of plasma lipemia. A decrease in oxygen availability in the myocardium may be responsible for the angina which can be induced by postprandial lipemia.

Summary

The effect of varying levels of lipemia upon tissue oxygen tension has been investigated in human subjects with normal and decreased peripheral blood flow. Oxygen tension of the skin was determined during rapid clearing of lipemia to avoid the difficulties inherent in prolonged study over the several hours of increasing lipemia following a fat meal. Regardless of whether peripheral blood flow was normal or decreased, a mean increase of 21.7 per cent in skin oxygen tension occurred during heparin-induced clearing of plasma turbidity. In addition, skin oxygen tension increased during the spontaneous decline of lipemia in 1 subject. Oxygen tension was not increased after a saline placebo injection during lipemia or following heparin injections in subjects with "clear" fasting serum.

The observed increase could not be attributed to changes in blood flow. Skin temperature remained stable during the experiments and the subject's response could not be correlated with skin blood flow as measured by the vasodilatation test. The increase in tissue

oxygen tension that occurs during clearing of plasma seems most probably to be due to increased diffusion of oxygen to or from the erythrocytes.

Acknowledgment

We are indebted to Miss Julia Van Horn, Dietitian, Hospital of the University of Pennsylvania, for her assistance in this study.

Summario in Interlingua

Le effecto de varie nivellos de lipemia super le tension de oxygeno tissular esseva investigate in subjectos human con normal e reducite fluxos de sanguine peripheric. Le tension de oxygeno del pelle esseva determinate durante le rapide claration de lipemia pro evitar le difficultates inherente in le prolongate studio a transverso le plure horas de crescente lipemia post un repasto grasse. Sin reguardo a si le fluxo de sanguine peripheric esseva normal o reducite, un augmento medie de 21,7 pro cento occurreva in le tension oxygenic del pelle durante le heparino-inducite claration del turbiditate del plasma. In plus, le tension oxygenic del pelle cresceva durante le declino spontanee del lipemia in un del subjectos. Le tension de oxygeno non esseva augmentate post le injection de un placebo salin durante le lipemia o post injectiones de heparina in subjectos con sero "clar" in stato jejun.

Le observate augmento non poteva esser attribuite a alterationes del fluxo de sanguine. Le temperatura del pelle remaneva stabile durante le experimentos, e le responsa del subjecto non poteva esser correlationate con le fluxo de sanguine in le pelle como illo esseva mesurate per le test del vasodilatation. Le augmento del tension de oxygeno tissular que occurre durante le claration del plasma es probabilissimemente causate per un augmento del diffusion de oxygeno ad o ab le erythrocytos.

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Direct-Reflection Oximetry in Routine Cardiac Catherization

By K. K. Bossina, M.D., G. A. Mook, M.D., and W. G. Zijlstra, M.D.

EARL H. WOOD was the first to stress the desirability of immediate oxygen saturation readings during diagnostic cardiac catheterization.[1, 2] The direct availability of oxygen saturation values together with pressure tracings and fluoroscopy leads to a more dynamic catheterization, in which each step is partially determined by the data already obtained. During the last 3 years we have been using a reflection cuvette oximeter providing immediate saturation values in some 200 cardiac catheterizations. This type of direct oximetry proved to be a remarkable asset. It simplified diagnosis, saved much work, and reduced blood loss to a negligible minimum. After a brief outline of apparatus and methods and a short survey of our results, this paper presents a discussion of selected cases in which direct oximetry provided a quick and accurate diagnosis, whereas the conventional sample methods most probably would have failed to yield the necessary information.

Principles and Methods

All photometric methods for determination of the oxygen saturation of blood are based on the difference in light absorption between hemoglobin and oxyhemoglobin: in the spectral range of 600 to 700 mμ hemoglobin absorbs much more light than oxyhemoglobin does. Most oximetric methods[2–6] measure variations in light transmission; Brinkman and Zijlstra[7] in 1949 started measuring light reflection and developed a number of oximetric methods based on this principle.[8] The main advantage of this approach is that light reflection is under certain conditions largely independent of the total hemoglobin concentration of the blood and thus is, within certain limitations, solely dependent on one variable, the oxygen saturation. Therefore reflection methods can be 1-color methods.

From the Department of Pediatrics and the Physiological Institute, University of Groningen, Netherlands.

The CC oximeter* is a reflection oximeter that is especially designed for cuvette oximetry during cardiac catheterization.[8–10] The catheter is connected to a small lucite cuvette. Half of this is filled with india ink and the other, entirely separate half receives the blood from the catheter. Rouleaux formation of the erythrocytes, which influences light reflection is prevented by a small magnetically driven stirring rod in the blood compartment. A reflectometer piece fits over the cuvette and may be alternately shifted over the black india ink part or over the blood sample just withdrawn through the catheter. The reflectometer is connected to a galvanometer (fig. 1) on which the scale has been calibrated in per cent oxygen saturation. The immediate readings give an exact indication of the differences in oxygen saturation between the samples and a fair approximation of the absolute values. After analysis of one or more samples by another method (Van Slyke's manometric method, spectrophotometric methods, hemoreflector[8]) the instantaneously obtained oxygen saturation values can later be converted into absolute values by simple addition or subtraction.

The oximeter cuvette is sterilized in a 1 per cent cetyltrimethylammonium bromide solution; just before connecting the cuvette to the catheter, it is flushed with sterile saline solution. We did not encounter any untoward effects (including febrile reactions) that could be traced to the use of the cuvette.

For each measurement (1) blood is drawn into the cuvette, (2) the stirring device is started, (3) the galvanometer is read, (4) the blood is reintroduced into the patient or stored in a syringe for analysis by other methods, (5) the cuvette is flushed with saline solution containing some heparin (10 mg./L.), and (6) the stirring motor is switched off. The entire procedure takes less than a minute.

The accuracy of the instrument is sufficient for clinical purposes. For a total of 228 measurements with 3 different CC oximeters, the standard deviation of the differences between the CC oximeter and the control instrument (hemoreflector,[8] spectrophotometer) was calculated at 1.68 per cent oxygen saturation.[9] No systematic difference was found.

The presence of the oximeter cuvette between

*Kipp and Sons Company, Delft, Netherlands.

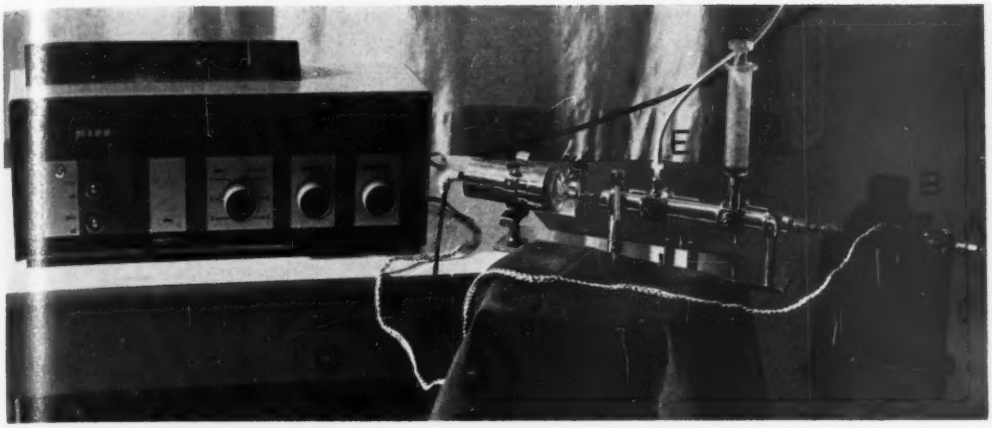

Figure 1

CC oximeter and additional apparatus. A, end of catheter; B, reflection oximeter on cuvette; C, magnetic stirring device; D, syringe for drawing blood through the cuvette; E, tube to bottle containing heparinized saline solution; F, Statham P 23 AA pressure transducer.

the catheter and the pressure transducer (fig. 1) has no influence on the shape or magnitude of the pressure curves.

Right heart catheterization was performed under light thiopental anesthesia; a conventional Cournand catheter, no. 6 or 7, was introduced through the great saphenous vein. The adjacent femoral artery was prepared and punctured under direct vision with a needle catheter especially designed for this purpose.[10, 11]

Results

From September 1956 to October 1959 direct oximetry was used in 195 cardiac catheterizations of infants and children, ranging from 3 months to 13 years of age. The average number of oxygen saturation readings per catheterization was about 15; in some cases 20 or more readings were made.

In nearly 70 per cent of our cases some type of shunt between the pulmonary and the systemic circuits could be demonstrated during catheterization. In the remainder the existence of a hemodynamically significant shunt was excluded by the oximetric data.

The following 6 cases have been selected because of the highly important part played by direct oximetry in the elucidation of an accurate and complete diagnosis. The catheterization data of these patients are presented in Table 1.

Abstracts of Cases

Case 1

G. R., a 10-year-old girl. Slightly enlarged heart at fluoroscopy. Normal heart sounds, no murmurs. Electrocardiogram: rR′ pattern in V_1. Radiologic findings: slight bulging of the superior vena cava, prominent pulmonary artery, pulmonary vascular engorgement. Diagnosis: pulmonary veins draining into superior vena cava.

Case 2

C. V., an 8-year-old girl. Recurrent respiratory infections, easy fatigue, and dyspnea on exertion. Thrill over jugular veins. Left ventricular impulse. First heart sound normal, second heart sound split and accentuated, third heart sound at apex; grade-III systolic murmur in second and third left intercostal spaces, grade-II to -III diastolic murmur in second and third left intercostal spaces. Electrocardiogram: incomplete right bundle-branch block, left ventricular hypertrophy. Radiologic findings: moderate left ventricular enlargement, prominent pulmonary artery, pulmonary vascular engorgement, slight hilar dance. Diagnosis: cerebral arteriovenous shunt, patent ductus arteriosus.

Case 3

A. H., a 2-year-old girl. Dyspnea on exertion, easy fatigue, and recurrent respiratory infections. Right ventricular impulse. Thrill at lower left sternal border. First heart sound normal, second heart sound slightly accentuated, third heart sound at apex; grade-IV systolic murmur in second and third left intercostal spaces, radiating to the back;

Table 1

Catheterization Data of Six Cases

Case		FA	IVC	SVC	RA	RV	PA	PV	LA	LV	Aorta
1. G.R. F 10 Pulmonary veins draining into SVC	pressure (mm. Hg)	115/60	4/1	5/1	4/1	27/0	20/6	10/6			
	% O_2 sat.	97	near RA 75 low 82	high 77, 77, 78 near RA 95, 94	81	81, 81	RPA 81	97 (draining into SVC)			
2. C.V. F 8 Cerebral AV shunt, patent ductus arteriosus	pressure (mm. Hg)	100/65	3/-2	4/0	3/-2	35/0	35/7				100/55
	% O_2 sat.	99	84	96 RJV 94, 97 LJV 96 RSV 76	92, 92	91, 92	conus 93 RPA 92 LPA 95, 96				99 (via patent ductus)
3. A.H. F 2 Sinus venosus variety of atrial septal defect	pressure (mm. Hg)	85/40	4/-2	4/-2	5/-2	50/0	35/7	10/0	10/0	100/0	
	% O_2 sat.	98	79	high 67 lower 71 near RA 85	high 97 TV 87	TV 88 mid 87	conus 89 RPA 89	99 (via ASD)	99	99	
4. M.W. M 1¾ Ventricular septal defect	pressure (mm. Hg)	80/65	5/-2	6/-4	4/-7	65/0	65/30 wedge 20/0				
	% O_2 sat.	99	80	high 66, 66 near RA 68, 69	mid 70, 71, 69 low 72 TV 68, 70, 72	TV 91, 94 mid 90, 91	conus 88 LPA 88				
5. P.O. M 5 mo. Atrial septal defect, ventricular septal defect	pressure (mm. Hg)	95/55	0/-5	1/-3	0	60/0	55/15				
	% O_2 sat.	95	73	high 70 near RA 68	mid 75 TV 76	TV 83 outflow 92, 90 shunt area 96	conus 91 RPA 91 LPA 92				
6. K.d.W. F 4 Complete transposition of great vessels	pressure (mm. Hg)	90/75	5/2	6/2	5/-1	90/0	20/10	15/10	8/5	38/0	
	% O_2 sat.	75	70	66, 65	75	mid 76 outflow 74, 75	conus 94, 94	100 (via ASD)	100	95	

Abbreviations: FA, femoral artery; IVC, inferior vena cava; SVC, superior vena cava; RA, right atrium; RV, right ventricle; PA, pulmonary artery; PV, pulmonary vein; LA, left atrium; LV, left ventricle; RJV, right jugular vein; LJV, left jugular vein; RSV, right subclavian vein; TV, tricuspid valve; RPA, right pulmonary artery; LPA, left pulmonary artery; ASD, atrial septal defect.

grade-II diastolic murmur at apex. Electrocardiogram: slight right ventricular hypertrophy. Radiologic findings: right atrium enlarged, pulmonary vascular engorgement, hilar dance. Diagnosis: sinus venosus variety of atrial septal defect.

Case 4

L. W., a 1 3/4-year-old boy. Soon tired and dyspneic after exercise. Recurrent respiratory infections. Right ventricular impulse. Thrill at lower left sternal border and apex. First heart sound normal, second heart sound split and slightly accentuated; grade-IV systolic murmur at lower left sternal border and apex. Electrocardiogram: right bundle-branch block, rR′ pattern in V_1, slight left ventricular hypertrophy. Radiologic findings: combined ventricular enlargement, pulmonary vascular engorgement, hilar dance. Diagnosis: ventricular septal defect.

Case 5

P. O., a 5-month-old boy. Tired and dyspneic at feedings. Recurrent respiratory infections. Dyspnea at rest. Thrill at lower left sternal border. Left ventricular impulse. First heart sound normal, second heart sound split and accentuated; grade-IV systolic murmur at lower left sternal border, radiating to the back. Electrocardiogram: first-degree atrioventricular block, left axis deviation, left ventricular hypertrophy. Radiologic findings: combined ventricular enlargement, pulmonary vascular engorgement, hilar dance. Diagnosis: atrial and ventricular septal defect.

Case 6

K.d.W., a 4-year-old girl. Cyanosis since birth. Soon tired and dyspneic. Clubbing. Right ventricular impulse. Thrill at lower left sternal border. First and second heart sounds normal, third heart sound at apex; grade-IV systolic murmur at left sternal border, slight radiation to the back. Electrocardiogram: P pulmonale, right ventricular hypertrophy. Radiologic findings: moderate right ventricular enlargement, slight left ventricular enlargement, pulmonary vascular engorgement. Diagnosis: complete transposition of great vessels.

Discussion

The routine application of a reflection cuvette oximeter allowing instantaneous determination of the oxygen saturation during cardiac catheterization appeared to be a considerable advance on the conventional sampling technic. The oxygen saturation values may be used for locating and directing the catheter tip; a virtually unlimited number of readings can be obtained from any area; the catheterization data can be given full consideration at a moment when additional data can easily be obtained; the blood used for the measurements can be reintroduced into the patient, the loss of blood thus being greatly reduced. After the introduction of direct oximetry it soon became customary to develop the diagnosis during the catheterization; in almost any case accurate insight into the existing malformations or disturbances could be gained in the course of the examination.

Cases 1 and 2 showed a remarkably high oxygen saturation in the superior vena cava. The source of highly saturated blood could in both cases easily be ascertained by successive saturation readings. In case 1 a sudden rise in oxygen saturation occurred when the catheter approached the right atrium, but in the right atrium itself lower saturation values were obtained. These findings exclude almost certainly the existence of an atrial septal defect and demonstrate an abnormally draining pulmonary vein. In case 2 exploration of the superior vena cava and the vessels draining into it revealed high saturation readings in both jugular veins. The postulated cerebral arteriovenous fistula was later demonstrated by cerebral angiography. The small but undeniable difference in oxygen saturation existing at the two sides of the pulmonary valve suggested a left-to-right shunt, which was thereupon proved by passing the catheter through a patent ductus.

In each case of atrial septal defect a series of oxygen saturation readings was taken from the superior vena cava and the right atrium in order to elucidate the exact location of the defect. In case 3 a rise in oxygen saturation was observed before the catheter reached the right atrium. On its way through the atrium the catheter passed through a region of high oxygen saturation values (97 per cent), but before reaching the tricuspid valve the saturation was at the level existing further throughout the right heart. These findings are typical for the sinus venosus variety of atrial septal defect. Attempts to pass through a septal defect were much more often successful after the introduction of direct oximetry, as is illustrated also by this case. In case 4 a primum defect was suspected. Repeated measurements, however, failed to

show any significant differences in oxygen saturation throughout the caval veins and right atrium, but revealed a considerable rise (22 per cent saturation) when the catheter tip passed the tricuspid valve, thus demonstrating a ventricular septal defect.

Extensive oximetric examination of infants is virtually impossible without the use of a direct method, allowing the reinjection of blood. With the aid of a cuvette oximeter, however, even the demonstration of combined atrial and ventricular septal defects (case 5), which usually requires many oxygen saturation readings, does not offer any special difficulty.

In case 6 the nature of the existing abnormalities was completely obscure before catheterization. The diagnosis (complete transposition of the great vessels) was built up step by step, mainly because of simultaneously obtained fluoroscopic and oximetric data.

Summary

A reflection cuvette oximeter providing instantaneous values has been used in a series of 195 cardiac catheterizations in infants and children. The introduction of this method had considerable influence on the entire catheterization procedure, since the direct availability of fluoroscopic, pressure, and oxygen saturation data allows development of an accurate and complete diagnosis during the catheterization. Six cases, selected because of the important part direct oximetry played in their elucidation, are discussed.

Summario in Interlingua

Un oxymetro reflexional a cuvette, providente valores instantanee, esseva usate in un serie de 195 catheterisationes cardiac in infantes e juveniles. Le introduction de iste methodo exerceva un considerabile influentia super le integre manovra catheterisational, proque le directe disponibilitate de dattos fluoroscopic, de pression, e de saturation oxygenic permitte le disveloppamento de un accurate e complete diagnose durante le catheterisation. Es discutite sex casos, selegite a causa del importante rolle de oxymetria directe in lor elucidation.

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Medicine absorbs the physician's whole being because it is concerned with the entire human organism.—Goethe.

I^{131}-Diodrast Studies in Unilateral Renal Disease

By JEROME B. BLOCK, M.D., GERALD J. HINE, PH.D., AND BELTON A. BURROWS, M.D.

With the technical assistance of Valentine Bikerman, B.S.

UNILATERAL renal disease is an infrequent cause of hypertension, occurring in less than 2 per cent of unselected hypertensive patients.[1] Such a small proportion of patients with unilateral renal disease respond to removal of the affected kidney that hypertension per se is not considered an indication for nephrectomy.[2] Hypertensive patients with unilateral renal arterial stenosis form an even smaller group, but their response is good to surgery performed before the development of extensive vascular disease involving the contralateral kidney.[3, 4] Ureteral catheterization or aortography may lead to earlier diagnosis and better surgical results in this condition, but associated technical difficulties, inconvenience, and complications of these procedures have limited their use in screening hypertensive patients in the incipient stages of the disease.[5, 6]

A simple and innocuous technic has been developed that demonstrates the excretion of I^{131}-Diodrast by each kidney.[7] This radioscopic method has been modified for the early diagnosis of unilateral renal disease by the use of carrier Diodrast and a ratiometer.[8] In this report the findings with I^{131}-Diodrast are compared with the results of intravenous pyelography, ureteral catheterization, and surgical exploration or autopsy.

From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, the Radioisotope and Medical Services, Boston Veterans Administration Hospital, and the Department of Medicine, Boston University School of Medicine, Boston, Mass.

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Materials and Methods

Two hundred and twenty-six hypertensive patients were studied with both I^{131}-Diodrast and intravenous pyelography; 49 of these were also studied by retrograde ureteral catheterization. When catheterization demonstrated a decrease in sodium concentration (at least 15 per cent) and volume (at least 50 per cent) of the urine from one kidney as compared with the other kidney, the results were interpreted as a "positive Howard test."[9] All other technically satisfactory results were termed negative; when insufficient urine was obtained from one kidney, the study was termed unsatisfactory. Forty were surgically explored: of these, 15 were subjected to unilateral nephrectomy, 3 underwent unilateral adrenalectomy, and the remainder submitted to lumbodorsal sympathectomy and renal biopsy. Except as noted in the text, all patients were studied with I^{131}-Diodrast prior to surgical exploration.

Patients drank about a quart of water in the hour prior to the I^{131}-Diodrast studies. They were then placed in a sitting position with radiation detectors directed horizontally at the renal areas normal to the skin surface. Monitoring sites were selected with the aid of available x-ray films. An intravenous infusion of 300 ml. of 5 per cent dextrose in water containing 1 Gm. of Diodrast was administered at a rate of 2 ml. per minute throughout the study; 2.5 ml. of 35 per cent Diodrast solution (1 Gm.) were injected directly into the rubber tubing of the infusion; this was followed by the rapid injection of 20 microcuries of I^{131}-Diodrast (approximately 0.1 mg.).*

The radioactivity that appeared in the separate renal areas was measured with 2 collimated scintillation detectors, a counting rate meter, a ratiometer† and a dual-channel linear recorder.‡ The counting rate in one renal area was recorded on one side of the recorder (the direct kidney tracing) and the ratio of the counting rate in one renal area to the total counting rate in both renal areas on the other side of the recorder (the ratiometer tracing) (fig. 1).

*Abbott Laboratories, Oak Ridge, Tenn.

†Baird-Atomic, Inc., Cambridge, Mass.

‡Texas Instrument Co., Houston, Tex.

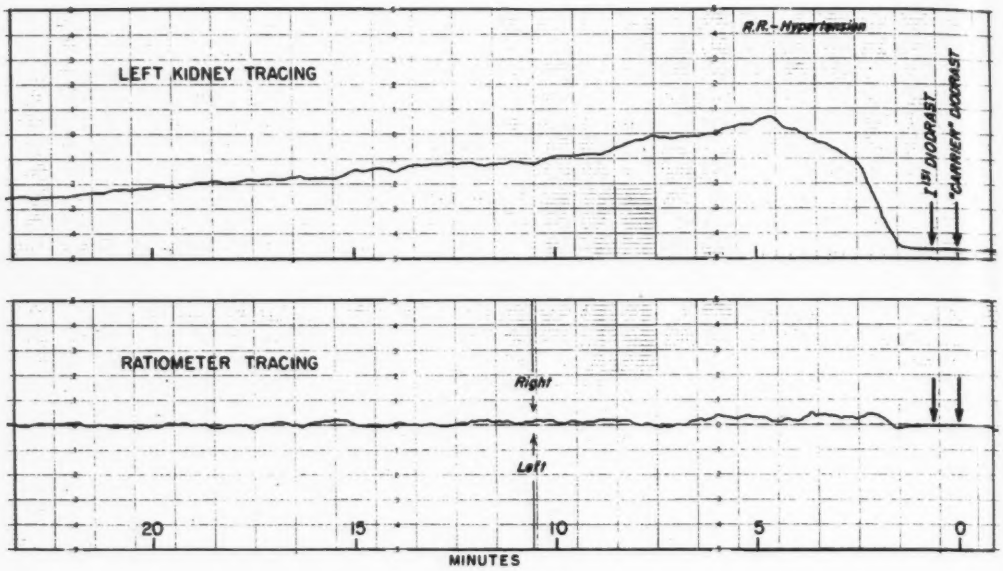

Figure 1

The normal tracings. The left kidney tracing is a direct recording of the counting rate of the left renal area. When both renal areas have equal counting rates, the ratiometer tracing is in the midline, indicating a ratio of right to left kidney radioactivities of 50/50. Deflections away from the midline indicate increased radioactivity in one renal area relative to the other.

For the ratiometer tracing, pulses from the sodium iodide crystals (1″ by 1″) were passed from probe-type preamplifiers through pulse-height selectors to scaling strips, and then into the ratiometer. The pulse-height selectors were set immediately below the absorption peak of the primary I^{131} gamma rays (364 kev.) to eliminate scattered secondary gamma rays. With a source at equal distance from the detectors, counting rates were balanced out at the midline of the ratiometer tracing by final adjustment of the pulse-height selectors. The ratiometer tracing recorded ratio of counting rate of one kidney to sum of counting rates of both kidneys, with a time constant dependent on the counting rates. This minimized statistical variation of plotted ratios.

From the direct kidney tracing, replotted on semi-logarithmic paper, a rate of uptake of I^{131}-Diodrast by one kidney was derived in the following manner (fig. 2*A*). Slope of the excretory phase was extended back to its intercept with the ordinate. At 20-second intervals following appearance of radioactivity in the renal area, recorded uptake was subtracted from the extended excretory slope and the difference was plotted. The half-time value in seconds of the straight line so obtained was termed "T½ uptake." "T½ excretion" was derived from the excretory slope, and the time required to reach peak uptake was also noted. No correction was attempted for extrarenal and background radioactivity.

From the ratiometer tracing, ratios of counting rates of the separate kidneys could be derived at selected times after the dose (fig. 1 and 2*B*). With equal counting rates in the 2 kidneys, the plotted ratio of one counting rate to the combined counting rates was 0.5 (midline on the graph). Differences in the counting rates of the separate kidneys were shown by a shift in the ratiometer tracing away from the midline. The direction of this shift (right or left) was determined by the placement of the detectors in relation to a unilaterally diseased kidney. Percentages of total counting rate contributed by each kidney could be determined from the graph at selected intervals. Ratios of the 2 counting rates were then expressed as a ratio of these percentages. An index of any change that occurred in one counting rate relative to the other, shown by a change in this ratio, was derived as follows. Near peak uptake in the direct kidney tracing, ratio "A" was determined by placing the higher percentage in the numerator if an initial shift in the ratiometer had occurred at this point. A straight line was drawn from this point along

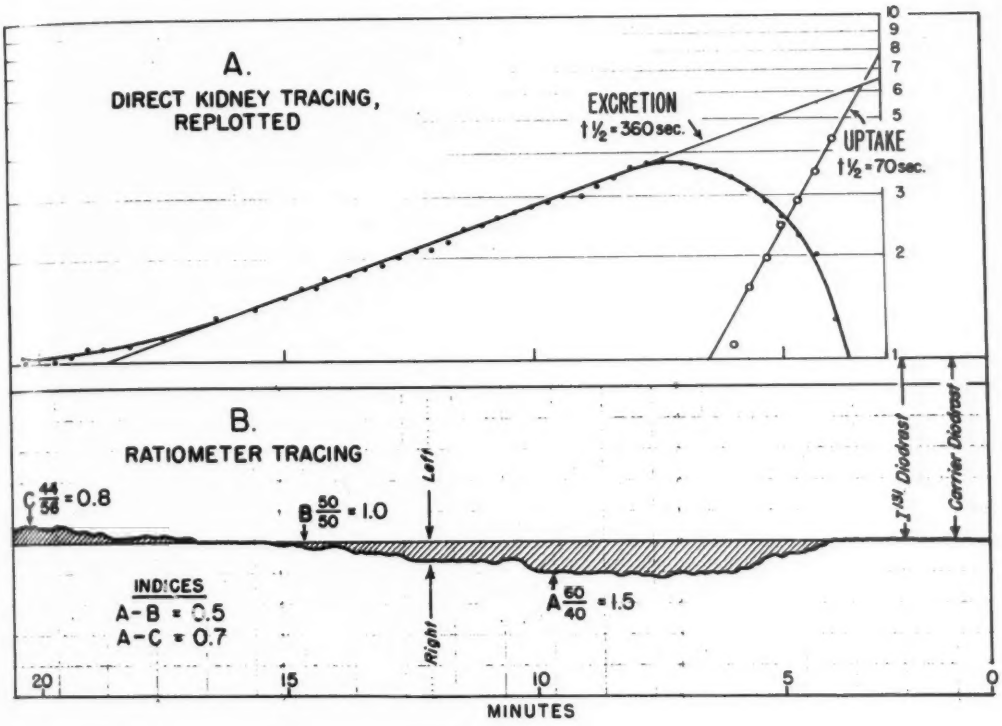

Figure 2

Determination of "T½ uptake," "T½ excretion," and the indices of secondary shifts of the ratiometer. A. On semi-logarithmic paper a straight line for excretion is obtained and used to determine T½ uptake. B. The hatched area emphasized differences between kidneys (cf. fig. 1). At point "A" the left kidney contained 60 per cent of the total activity in both renal areas, and the ratio between the kidneys was 1.5. At point "B" this ratio was 1.0, and at point "C," 0.8. The ratios at "B" and at "C" are subtracted from the ratio at "A" to obtain indices of the observed secondary shift in the tracing.

the ratiometer tracing over a 5-minute interval and the ratio was again determined (at B). At the point of greatest subsequent change, the ratio was also determined (at C). Ratio at A minus ratio at B (A-B) and ratio at A minus ratio at C (A-C) were calculated as indices of secondary shifts occurring after peak uptake in the direct kidney tracing.

The tracings were continued for 30 minutes, at which time a urine sample was collected to determine the per cent of the dose excreted.

Results

Interpretation of the Tracings

Simple inspection of the tracings usually sufficed to rule out or in a unilateral renal lesion. In the absence of unilateral renal disease, there was good agreement between "T½ uptake" of the direct kidney tracing and the 30-minute urine excretion of I^{131}-Diodrast ($r = 0.873$, fig. 3). The uptake also correlated well with the time of peak radioactivity ($r = 0.93$). In patients without evidence of unilateral renal disease, little deflection of the ratiometer tracing from the midline was observed, reflecting a similar uptake and excretion of I^{131}-Diodrast by the 2 kidneys (fig. 1).

An initial shift of the ratiometer indicated a diminished uptake of I^{131}-Diodrast by one kidney as compared with the other. Without a significant difference in the subsequent rates of excretion by the 2 kidneys, a relatively con-

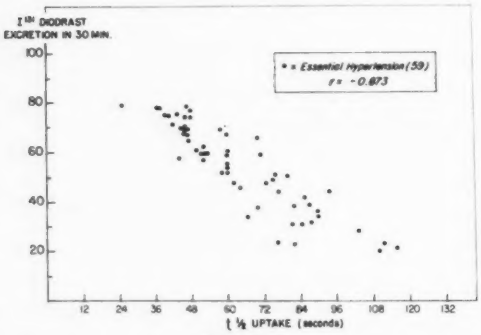

Figure 3

Comparison of T½ uptake and urine excretion of I^{131}-Diodrast. Values for a T½ uptake derived from direct kidney tracings are compared with the I^{131}-Diodrast excretion in the urine in 30 minutes. Some low excretion results may have been due to errors in bladder emptying. This correlation did not hold in patients with unilateral renal disease.

stant ratiometer recording was obtained after peak uptake (type 1) (fig. 4). Such differences in uptake usually correlated well with differences in I^{131}-Diodrast excretion determined by bilateral ureteral catheterization, but similar tracings were also seen with differences between the kidneys in counting geometry. Type 1 tracings were not observed with proved unilateral renal arterial stenosis.

Minor secondary shifts in ratiometer tracings could be observed late in the excretion phase, due to decreasing renal radioactivity relative to tissue background radioactivity, in the absence of unilateral renal disease.[8] An obvious secondary shift occurring soon after peak uptake, with or without an initial shift of the ratiometer, indicated delayed excretion of I^{131}-Diodrast by one kidney compared to the other (type 2) (fig. 5). All patients with proved unilateral renal arterial stenosis had type 2 tracings.

Correlation of Calculated Indices with Ureteral Catheterization, Surgical Exploration, or Autopsy

All patients with secondary shift indices (A-C) less than 0.3 showed no evidences of relative unilateral renal disease by ureteral catheterization studies, surgical exploration, or autopsy; therefore, such I^{131}-Diodrast results were considered normal (fig. 6). Patients with either proved unilateral renal arterial stenosis or parenchymal disease always had (A-C) indices of 0.3 or greater, attributed to relative retention of I^{131}-Diodrast in the kidney with diminished urine flow, which were therefore considered abnormal. Except for 1 patient, the index (A-B) was equally discriminatory. Such patients demonstrated higher indices with higher urine flows, due presumably to greater differences in the washout of I^{131}-Diodrast from the separate kidneys (fig. 7). In patients with a "non-functioning" kidney by intravenous pyelography, calculated indices were even higher (table 1).

Abnormal I^{131}-Diodrast results were seen with a difference between the kidneys in urine flow, with or without differences in urine sodium concentration. Calculated indices of differences in rates of I^{131}-Diodrast excretion by the 2 kidneys were compared with differences in urine flow noted at the time of ureteral catheterization (fig. 8). Although the two sets of observations were made under different conditions, the indices usually predicted the observed urine flow differences between kidneys. Exceptions occurred in patients with obstructive uropathies in whom the ureteral catheter was passed beyond the site of obstruction.

Among 23 patients with normal I^{131}-Diodrast results, ureteral catheterization revealed no significant differences between the kidneys in sodium and water excretion (table 2). Six patients with such negative Howard tests had type 1 I^{131}-Diodrast results. Four of the 8 patients with type 2 I^{131}-Diodrast results and negative Howard tests (table 2), with differences between the kidneys in urine flow without differences in urine sodium concentration, had renal parenchymal disease (K.L., D.G., G.M., V.H., table 1). Of the 4 remaining patients with type 2 I^{131}-Diodrast results and differences in urine flow without differences in urine sodium concentration, 2 had abnormalities of calyceal system, another had a displaced right kidney, and the fourth on 2 subsequent occasions, had normal I^{131}-Diodrast results (S.B., B.P., R.G., V.K., table 1).

All 7 patients with positive Howard tests

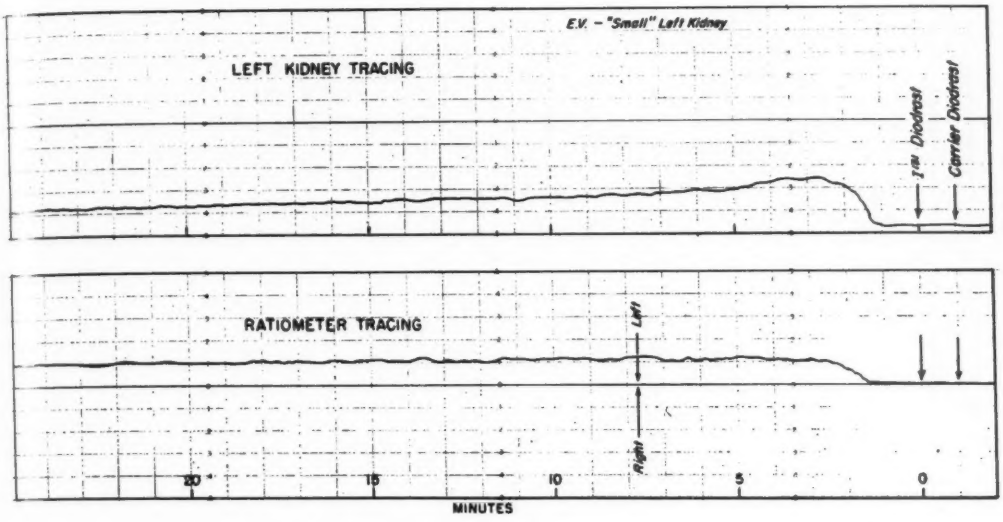

Figure 4

The type 1 tracing, indicating an initial shift in the ratiometer. Approximately 60 per cent of the radioactivity was in the right renal area.

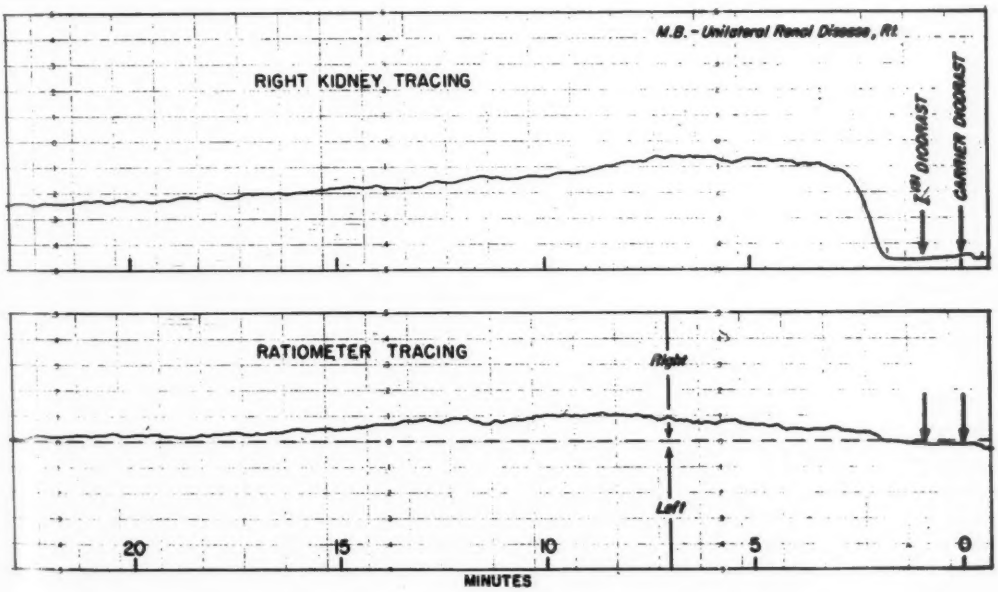

Figure 5

The type 2 tracing, indicating a secondary shift in the ratiometer. Both diminished uptake and delayed excretion of I^{131}-Diodrast by the affected kidney was observed (cf. fig. 4).

Table 1

Renal Data in Twenty-Two Patients

Subject	I^{131}-Diodrast results	Indices (A-B)	Indices (A-C)	Howard test	Intravenous pyelogram	Surgery	Pathology	Comment
A. L.	Type 2 positive rt. renal disease	1.1	1.9	unsatisfactory	poor functioning rt. kidney	rt. nephrectomy	atrophic kidney	good* response but 2 hypotensive CVA
S. B.	Type 2 positive rt. renal disease	0.3	0.8	negative	none, allergic			bilat. uretero-pelvic obstruction by retrograde study
H. D.	Type 2 positive rt. renal disease	**1.1**	**1.2**		small non-functioning rt. kidney	rt. nephrectomy	thrombosis rt. renal artery	no B. P. response 1/2-yr. follow-up
F. G.	Type 2 positive rt. renal disease	0.4 1.0	0.3 1.2	positive on rt.	normal	rt. nephrectomy	anomalous arterial supply	good* response 1-yr. follow-up
R. G.	Type 2 positive rt. renal disease	1.2	0.7	negative	low rt. kidney			
V. K.	1. Type 2 positive rt. renal disease 2. negative 3. negative	0.5 0.1 0.1	0.7 0.2 0.2	negative	normal			
A. W.	Type 2 positive rt. renal disease	0.9	1.2	unsatisfactory	non-functioning rt. kid.	rt. nephrectomy	hydronephrosis	no response 6-mo. follow-up
C. R.	Type 2 positive rt. renal disease	0.5	0.8	positive on rt.	atrophic upper pole rt. kidney	rt. nephrectomy	infraction upper pole rt. kidney	good* response 1-mo. follow-up
D. F.	Type 2 positive rt. renal disease	1.6	0.4	positive on rt.	normal	rt. nephrectomy	anomalous	good* response 1-mo. follow-up
A. H.	Type 2 positive rt. renal disease	0.2 0.4	0.5 0.4	positive on rt.	small rt. kidney with good functioning	rt. nephrectomy	juxtaglomerular hypertrophy	good* response 1-mo. follow-up
S. C.	Type 2 positive lt. renal disease	0.4	0.7	unsatisfactory	non-functioning lt. kidney	lt. nephrectomy	thrombosis lt. renal artery	no B.P. response 6-mo. follow-up
D. G.	Type 2 positive lt. renal disease	0.4	1.9	negative	delayed excretion lt. kidney			water and creatinine excretion decreased, lt. kidney
L. D.	Type 2 positive rt. renal disease	0.4	2.1		non-functioning rt. kidney	rt. nephrectomy	hydronephrosis	no B.P. response to 6-mo. follow-up
G. M.	Type 2 positive rt. renal disease	0.2	0.7	negative	caliectasis on rt.			water and creatinine excretion decreased, rt. kidney
K. L.	Type 2 positive rt. renal disease	0.4	0.6	negative	small rt. kidney with diminished function			water excretion decreased, rt. kid.

M. B.	Type 2 positive rt. renal disease	0.3	0.5	positive on rt.		rt. nephrectomy	intimal hyperplasia rt. renal artery	good* response to 4-mo. follow-up
[illegible]	[illegible] rt. renal disease	[illegible]		positive on rt.	normal	rt. nephrectomy	constriction rt. renal artery	good* response 1-1/2 yr. follow up
C. W.	Type 2 positive lt. renal disease	2.0	2.4	unsatisfactory	poor functioning lt. kidney	lt. nephrectomy	thrombosis lt. renal artery	good* response 1/2-yr. follow-up
B. S.	Type 2 positive lt. renal disease	0.8	0.9	unsatisfactory	non-functioning lt. kidney	lt. nephrectomy	atrophic lt. kidney	? response to surgery 1 month
A. K.	Type 2 positive lt. renal disease	0.6	0.6	positive on lt.	small lt. kidney with normal function	lt. nephrectomy	intimal hyperplasia renal artery focal tubular atrophy and chr. pyelonephritis	good* response 1-mo. follow-up
V. H.	Type 2 positive rt. renal disease	0.9	1.1	negative	small rt. kidney with imperfect function	rt. nephrectomy	small kidney and decreased urine flow art., chronic pyelonephritis from rt. kidney	? B.P. response
B. P.	Type 2 positive rt. renal disease	0.5	0.5	negative	bifid pelvis and ureter on left			same 15 min. I^{131}-Diodrast excretion bilaterally

*Postoperative blood pressure below 150/100.

Figure 6

Comparison of secondary shift indices with ureteral catheterization (Howard test), surgery, or autopsy. Positive, negative, or unsatisfactory Howard tests were observed in patients with indices noted in the two columns on the left. In the two right-hand columns, pathologic differences between the kidneys or renal arteries are correlated with the indices. Patients with bilateral renal disease at autopsy or by biopsy were considered to have no differences between kidneys; in such patients, the direct kidney tracings were abnormal.

had abnormal I^{131}-Diodrast results. Five additional patients with abnormal I^{131}-Diodrast results had such extensive unilateral renal disease that no urine could be collected from the affected side (B.S., S.C., A.L., A.W., C.W., table 1).

Forty of the patients were surgically explored (table 3). Fifteen patients with unilateral renal disease at nephrectomy had abnormal I^{131}-Diodrast results. Among the 40 explored, 25 patients without surgically identified renal disease had normal I^{131}-Diodrast results. Among the 15 patients with unilateral lesions, 12 had abnormal intravenous pyelograms, while pyelograms of 3 were interpreted as being normal. Two of the 25 patients without surgically demonstrable disease had abnormal intravenous pyelograms.

Correlation of the I^{131}-Diodrast Results with Intravenous Pyelography

In 226 patients, intravenous pyelograms were available for comparison with the I^{131}-Diodrast results (table 4). One hundred and seventy-one of the 174 patients with intra-

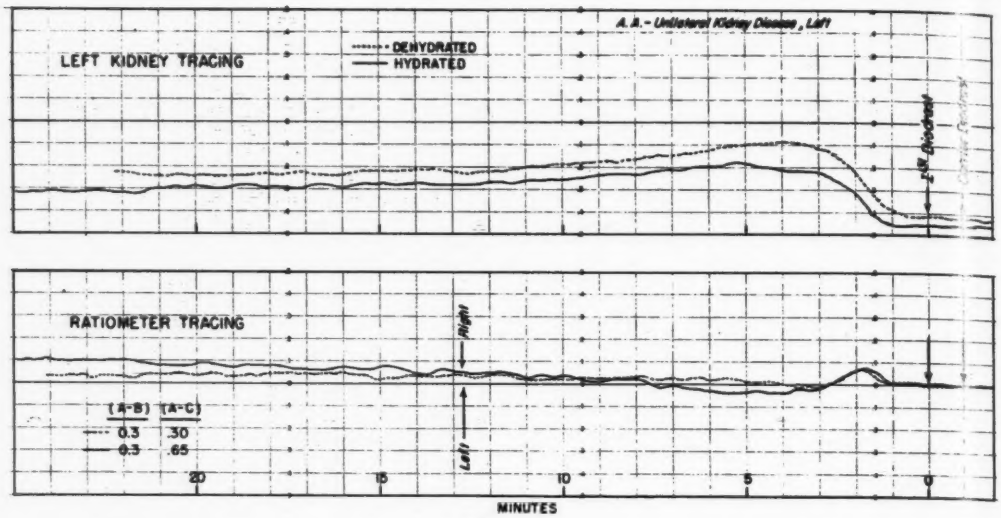

Figure 7

Effects of hydration on calculated indices of secondary shift. Hydration augmented differences in the rate of excretion of I^{131}-Diodrast between kidneys as shown by the higher (A-C) index obtained.

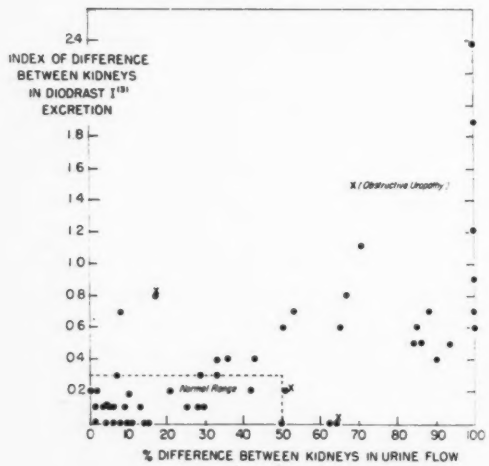

Figure 8

Calculated indices of difference between kidneys in I^{131}-Diodrast excretion plotted against the difference between kidneys in urine flow revealed at the time of retrograde catheterization.

venous pyelograms interpreted as normal had normal I^{131}-Diodrast results. Three patients with normal intravenous pyelograms and abnormal I^{131}-Diodrast results were subsequently shown to have unilateral renal arterial stenosis with a good response to nephrectomy (F.G., D.F., and E.A., table 1).

Table 2

Comparison of Diodrast and Howard Test

Number: 49	I^{131}-Diodrast results Negative	Type 1	Type 2
Howard test:			
Negative	23	6	8
Positive	0	0	7
Unsatisfactory	0	0	5

Of the 52 patients with abnormal intravenous pyelograms 46 had abnormal I^{131}-Diodrast results. Of 6 patients with abnormal intravenous pyelograms and normal I^{131}-Diodrast results, 5 had "small" kidneys demonstrated by pyelography. Three of these showed type 1 I^{131}-Diodrast results, and unilateral renal arterial stenosis was subsequently ruled out. Two of these 5 patients with normal I^{131}-Diodrast results were explored and the kidneys found to be grossly normal. The sixth patient had intravenous pyelograms that suggested differences in kidney function, but with normal I^{131}-Diodrast results; at the time of subsequent splanchnicectomy, bilateral

Table 3

Relation of Renal Tests to Findings at Surgery

Number: 40	I^{131}-Diodrast results		Howard test			Intravenous pyelogram	
	Positive	Negative	Positive	Negative	Unsatisfactory	Positive	Negative
Surgical exploration:							
Unilateral renal lesion	15	0	7	1	5	12	3
No unilateral lesion	0	25	0	9	0	2	23

pyelonephritis and grossly normal renal arteries were observed.

Two of the 46 patients with abnormal I^{131}-Diodrast results (type 2) had unilateral small but "normally functioning" kidneys by intravenous pyelography, and favorably responded to nephrectomy (A.H., A.K., table 1). The others all had differences in function indicated by intravenous pyelography.

Because of the occasional disagreement between the results of intravenous pyelography and I^{131}-Diodrast studies, the latter were repeated in patients with type 2 abnormalities, with use of a dose of carrier I^{127}-Diodrast (20 Gm.) comparable to the doses of contrast media used for intravenous pyelography. The type 2 abnormality diminished with the larger dose of Diodrast (figs. 9 and 10).

Discussion

Experimental findings have suggested that reduced urine flow and sodium concentration may be the initial functional abnormality of a kidney with partial constriction of a main renal artery, and that this may occur without changes in inulin or para-amino hippurate clearances.[10] The clinical counterpart may be occasionally observed in patients in whom the renal blood flow may not be reduced into subnormal ranges (F.G., Appendix), although clearance data in the patient group is not available.[5, 11]

It has been demonstrated in normal subjects that the rate of I^{131}-Diodrast excretion reflects changes in urine flow.[8] Two patients in the present report with unilateral renal arterial stenosis had differences between the kidneys in rates of I^{131}-Diodrast excretion without obvious differences in "uptake" of I^{131}-Diodrast (F.G., fig. 11 and D.F., (fig. 12).

Table 4

Comparison of Diodrast Tests and Pyelogram

Number: 226	I^{131}-Diodrast results	
	Negative	Positive
Normal intravenous pyelogram	171	3
Abnormal intravenous pyelogram:		
Small kidney	5	2
Difference in function between kidneys	1	44

In other patients a reduced uptake of I^{131}-Diodrast suggested impairment of renal blood flow in one kidney. The rate of uptake of I^{131}-Diodrast has been shown to correlate with the 30-minute excretion of I^{131}-Diodrast, and probably is dependent on both renal blood flow and adequacy of the Diodrast transport system.[8] In the absence of renal extraction ratios, however, the precise relationship between the uptake of I^{131}-Diodrast and renal blood flow cannot be determined. Therefore, in patients with unilateral renal arterial stenosis and hypertension, a screening procedure sensitive to the early changes in urine flow as well as the later changes in renal blood flow is of value.

In addition to our 3 patients, 15 others with proved unilateral partial obstruction of a renal artery have had normal intravenous pyelograms.[5, 6, 12] Difference in uptake of I^{131}-Diodrast by the 2 kidneys was less following a large dose of carrier I^{127}-Diodrast than with a small dose (figs. 9 and 10). During the I^{131}-Diodrast procedure, plasma levels are below tubular maximum secretory capacity. With doses of I^{127}-Diodrast or other contrast media used for intravenous pyelography, plasma levels transiently exceed maximum

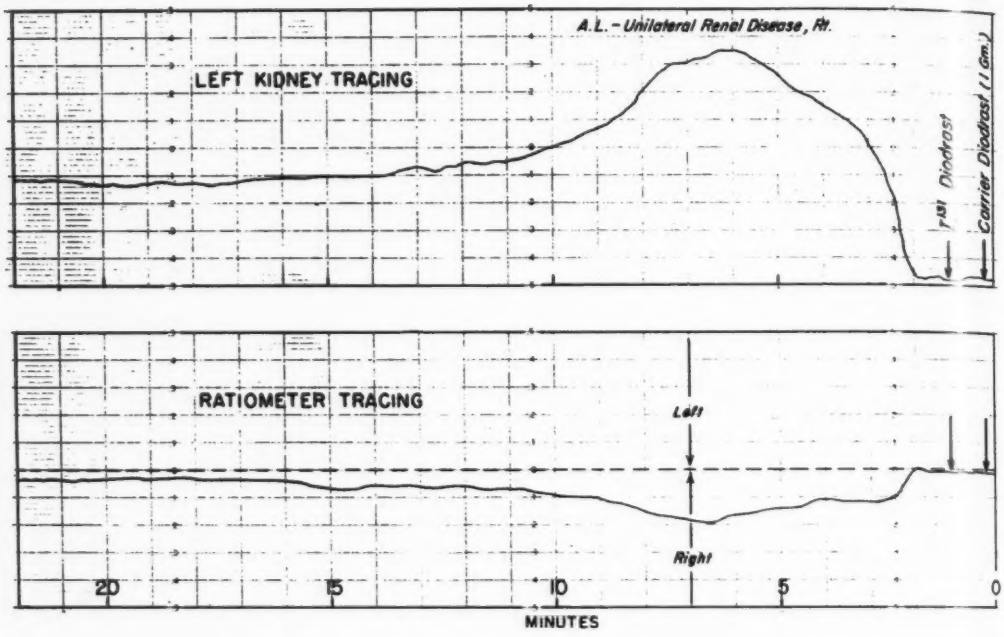

Figure 9

Tracing of patient A. L. with proved unilateral renal arterial stenosis, with a 1-Gm. dose of carrier Diodrast.

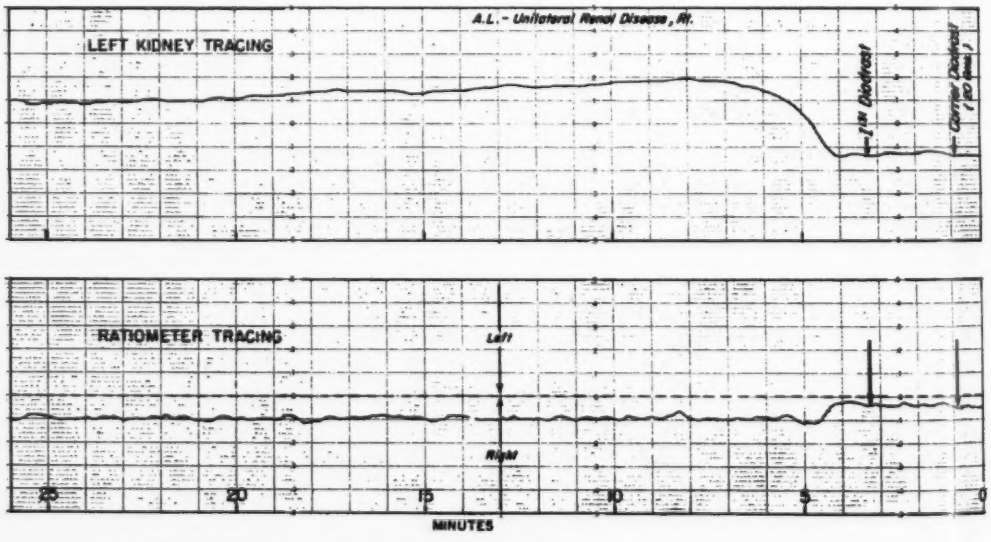

Figure 10

Tracing from patient A. L. obtained with a 20-Gm. dose of carrier Diodrast. Differences in excretion of I^{131}-Diodrast by the 2 kidneys are less obvious than in figure 9.

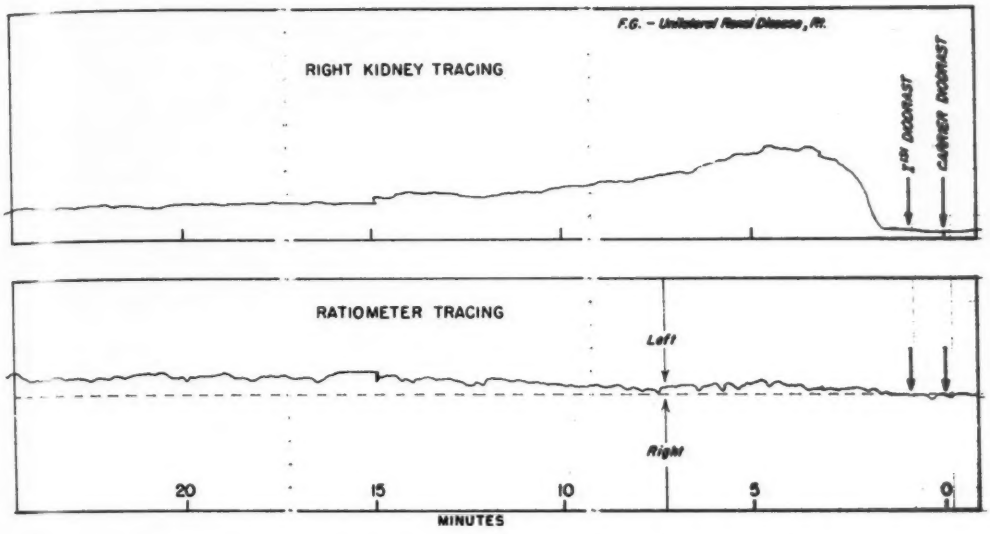

Figure 11

Type 2 tracing in patient F. G., Appendix. Little difference in uptake of I^{131}-Diodrast between kidneys was detected, but a delay in excretion from the right kidney was observed (cf. fig. 1).

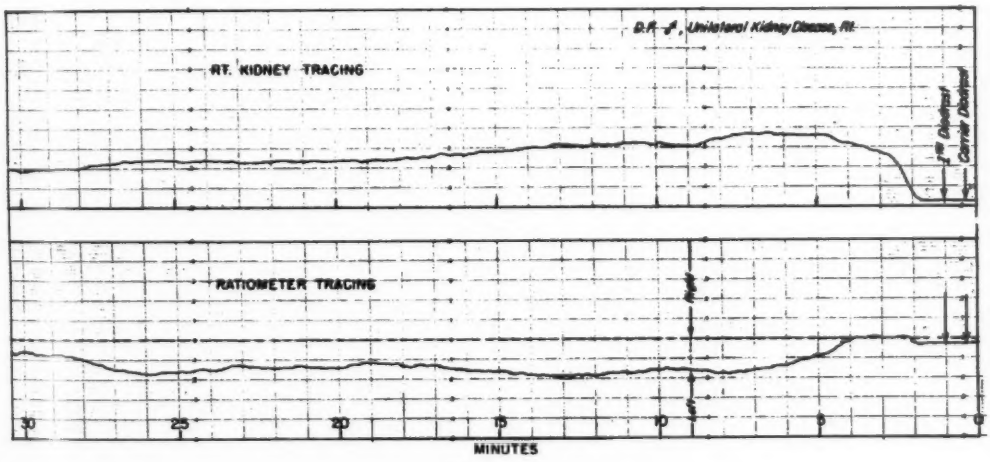

Figure 12

Type 2 tracing in patient D. F., Appendix. No difference in uptake of I^{131}-Diodrast between kidneys was noted in the first minutes of the test, but a marked delay in excretion from the right kidney was observed.

secretory capacity of the tubules. Therefore, relatively greater amounts of Diodrast may appear in the urine as a result of glomerular filtration during pyelography than during I^{131}-Diodrast studies.

In addition, clearance studies of contrast media used for intravenous pyelography have shown considerable variation in the degree to which these compounds are excreted by the tubules.[13, 14] In a study of hypertensive pa-

tients with bilateral and unilateral pyelonephritis in whom 13 kidneys were reported as normal by intravenous pyelography, there were 30 to 55 per cent reductions below anticipated effective renal plasma flow in 11 and in 10 there were also 30 to 45 per cent reductions in glomerular filtration rate.[15] Three of the 4 kidneys studied were noted to have decreased Tm_{PAH} with normal intravenous pyelograms.

The results in patient F.G. (Appendix) suggest certain differences between differential phenolsulfonphthalein excretions determined during ureteral catheterization and the I^{131}-Diodrast results. Abnormalities in renal function that result only in transient delays in excretion may not be apparent with single 30-minute urine collections from each ureter. However, with constant external monitoring of renal radioactivity following I^{131}-Diodrast injection, such slight differences in excretion times may be detected.

The results with I^{131}-Diodrast are abnormal in unilateral renal disease due either to pyelonephritis or to renal arterial occlusion, and in advanced stages, these diseases could not be differentiated. All reported cases with a positive Howard test have had an impaired renal arterial supply.[5, 11] Several of our patients with abnormal I^{131}-Diodrast results had negative Howard tests and the affected kidney was not removed, so that an explanation of the abnormal results was not available. One patient with abnormal I^{131}-Diodrast results and a negative Howard test showed an equivocal response to nephrectomy. Several patients with positive Howard tests had renal arterial constriction in addition to pyelonephritis.

There have been reports of hypertensive patients with occlusive disease of a branch of a renal artery who had impaired urine flow from the affected kidney without a concomitant decrease in urine sodium concentration.[16] One of our patients had such a branch lesion (C.R., table 1) with a unilateral reduction in both urine sodium concentration and urine flow. It would appear that arterial lesions sufficient to produce a relative fall in urine volume alone should be detected in the excretion phase of the I^{131}-Diodrast study.

Although the duration of follow-up of the nephrectomized patients in our study is inadequate for long-term evaluation of the results, several points may be made. With early diagnosis, before unilateral renal arterial stenosis had led to gross changes detectable by intravenous pyelography, the results of nephrectomy were excellent. Patients with more advanced unilateral renal disease did less well following surgery (H.D., S.C., B.S., A.W., L.D., table 1). Early diagnosis of patients with unilateral renal arterial stenosis is therefore important.

Summary

A procedure utilizing I^{131}-Diodrast with carrier Diodrast and a ratiometer has been evaluated for the early diagnosis of unilateral renal disease.

Relative differences in function between kidneys demonstrated by this procedure correlated well with findings at surgical exploration or autopsy.

In 3 patients with unilateral renal arterial stenosis who had normal intravenous pyelograms, I^{131}-Diodrast results were abnormal.

Although normal I^{131}-Diodrast results may rule out unilateral renal disease, an abnormal result with I^{131}-Diodrast may be seen with any lesion resulting in urine flow differences between kidneys.

Acknowledgment

Acknowledgments are due to Medical and Urological Staffs of the Peter Bent Brigham Hospital, the New England Medical Center, and the Providence Veterans Administration Hospital for their helpful cooperation in referring patients and furnishing clinical data included in this report.

Appendix

Case 1

F.G., a 38-year-old white man was admitted to another hospital for evaluation of hypertension of 3 months' duration. Four months prior to admission during an insurance examination, the patient was told he had a normal blood pressure. Three months prior to admission, he noted an episode of periodic stiffness of his wrists and ankles and passed cloudy yellow urine. Frontal headaches

became prominent but there were no other symptoms. Thereafter he remained in good health until he consulted his physician concerning an upper respiratory infection, 2 weeks before admission. Because of a blood pressure of 210/120, hospitalization was advised.

There was no history of known cardiovascular or renal disease. The patient's mother was observed to have hypertension following a heart attack at the age of 71.

On physical examination the blood pressure was 180/120 in both arms without postural hypotension. Grade-2 hypertension retinopathy was described. The heart and lungs were normal. The abdomen was unremarkable and there was no costovertebral angle tenderness. Laboratory examination showed a normal hemogram; repeated urinalyses showed occasional 1 plus albuminuria and a normal urinary sediment. The serum electrolytes were normal. The electrocardiogram, chest x-ray, and intravenous pyelogram were interpreted as normal.

Prior to nephrectomy the patient remained hypertensive. Both Regitine and Etamon tests were negative. The Howard test, performed twice within a week's interval, disclosed markedly decreased sodium concentration and urine flow from the right kidney. There was no difference in phenolsulfonphthalein excretion from the 2 kidneys. I^{131}-Diodrast results demonstrated no difference in uptake, but significant delay in excretion by the right kidney with an (A-B) index of 0.4 and (A-C) of 0.5 (fig. 11).

The right kidney was explored and removed. No fall in blood pressure occurred upon clamping the renal artery. Four small arteries supplied the kidney, which was otherwise normal pathologically. After the first postoperative day, the patient's blood pressure fell to normotensive levels and has remained in this range during a 7-month follow-up period.

Case 2

D.F., a 49-year-old white male engraver was admitted for evaluation of hypertension of 6 months' duration. The patient was in good health until 6 months prior to admission, when nervousness and headaches appeared. A physician was consulted, and the patient's blood pressure was noted to be 240/145. He did not respond to medical therapy. There was no family history of hypertension or renal disease. Urinary symptoms were absent. Episodes of dizziness and sweating were noted after taking a highball.

On physical examination the blood pressure was 250/110 lying and 274/140 standing, but postural hypotension was noted on several occasions. Funduscopic examination showed grade 2 hypertension and grade 1 arteriosclerotic retinopathy. The lungs and heart were normal. No abdominal masses were felt. There was no costovertebral angle tenderness. There was atrophy of all muscle groups and shortening of the left arm due to childhood poliomyelitis.

The hemogram was normal. Urinalyses showed repeated 1 plus to 2 plus albuminuria, with a rare hyaline and finely granular cast. The excretion of phenolsulfonphthalein was normal. The blood urea nitrogen was 28 mg. per cent and the serum creatinine was 0.2 mg. per cent. Serum electrolytes were normal. The electrocardiogram showed left ventricular hypertrophy. An intravenous pyelogram was read as normal.

There was good blood pressure response to sedation. A Regitine test was negative. I^{131}-Diodrast results were abnormal, showing a marked decrease in the rate of excretion by the right kidney, with an (A-C) index of 1.9 (fig. 12). A Howard test was positive for right renal disease. At surgical exploration, 2 tiny right renal arteries were noted, which did not pulsate. The left renal artery was normal. Clamping the right renal pedicle was without effect on the blood pressure. The right kidney was removed. Pathologic examination showed slight arteriolar nephrosclerosis, focal calcification of the medulla, and tubular vacuolization similar to that seen with hypokalemia. In the first postoperative week, the blood pressure fell to levels of 190 to 160/110 to 80. The blood urea nitrogen was 27 mg. per cent. The patient felt well throughout the period of nitrogen retention and at the time of discharge, 18 days after nephrectomy, the blood pressure was 160 to 140/100 to 90.

Summario in Interlingua

Es evalutate un methodo utilisante Diodrast a I^{131} con Diodrast como portator e un ratiometro in le precoce diagnose de morbo renal unilateral.

Le relative differentias functional inter le duo renes, demonstrate per medio de iste methodo, monstrava un alte correlation con le constatationes al exploration chirurgic o al necropsia.

In 3 patientes con stenosis reno-arterial unilateral, le pyelogramma intravenose esseva normal, sed le resultatos del studio con Diodrast a I^{131} esseva anormal.

Ben que normal resultatos obtenite con Diodrast a I^{131} exclude le presentia de morbo renal unilateral, anormal resultatos pote obtener se con Diodrast a I^{131} in casos de non importa qual lesion que causa un differentia del fluxos urinari ab le duo renes.

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The critical sense and skeptical attitude of the Hippocratic school laid the foundation of modern medicine on broad lines, and we owe to it: first, the emancipation of medicine from the shackles of priestcraft and of caste; secondly, the conception of medicine as an art based on accurate observation, and, as a science, an integral part of the science of man and of nature; thirdly, the high moral ideals expressed in that most memorable of human documents, the Hippocratic oath; and fourthly, the conception and realization of medicine as a profession of a cultivated gentleman.—SIR WILLIAM OSLER. *Aphorisms from His Bedside Teachings and Writings.* Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 114.

Left Heart Catheterization by the Transseptal Route

A Description of the Technic and Its Applications

By JOHN ROSS, JR., M.D., EUGENE BRAUNWALD, M.D., AND ANDREW G. MORROW, M.D.

LEFT ATRIAL pressure was first recorded in man by Cournand et al. during cardiac catheterization in a patient with an atrial septal defect. Their report in 1947[1] proved the feasibility of passing a catheter from the right atrium to the left when an interatrial communication was present. When operations for the correction of rheumatic mitral and aortic stenosis were undertaken, the value of preoperative measurements of pressure in the left atrium and left ventricle soon became apparent. In these patients, without intracardiac communications, it was necessary to devise other means of access to the left-sided chambers of the heart. The methods of transbronchial and posterior percutaneous left atrial puncture[2-6] were found to be practical technics for the measurement of left atrial pressure and each was extended to permit left ventricular and aortic catheterization as well. It was found that left ventricular pressure could also be measured by direct transthoracic puncture of this chamber[7] or by means of a catheter passed into it, in a retrograde fashion, from a peripheral artery.[8] The relative advantages and disadvantages of these various methods of left heart catheterization have recently been presented in detail[9] and experience with them has indicated that none is ideal in all respects.

A cardiac catheter, when introduced from the saphenous vein, can invariably be passed through an interatrial septal defect or patent foramen ovale, if such a communication is present. This course of the catheter suggested the possibility to Dr. Emilio Del Campo, during a visit to the National Heart Institute, that the intact interatrial septum could be crossed in the region of the fossa ovalis and provide another means of access to the left atrium. It appeared to us that this could be accomplished by a suitably curved needle passed through a catheter positioned against the septum. In an experimental study in dogs[10, 11] left atrial puncture by this technic was found to be simple and without hazard. Transseptal left heart catheterization was then applied in clinical studies and preliminary experiences with it were encouraging.[12-15] The method has now been employed in 130 patients with various forms of heart disease. The present report describes in detail the instruments employed in transseptal left heart catheterization, the technics of the procedure, and some of its applications in cardiovascular diagnosis and clinical investigation.

From the Clinic of Surgery, National Heart Institute, Bethesda, Md.

Dr. Ross' present address: Department of Surgery, Columbia-Presbyterian Medical Center, New York, N. Y.

Material and Method

Equipment

Shortened Right Heart Catheter

The catheter through which the no. 17-gage transseptal needles are passed is a no. 8 Aorto-catheter (61 cm. in length) having an extruded Nylon core.* A removable adapter (Tuohy-Borst)* is attached to the proximal end of the catheter. The transseptal needles may vary slightly in length and the catheter should be compared with the transseptal needle with which it is to be used; the proximal end of the catheter is cut so that it is 2 cm. shorter than the needle. The length of the catheter then corresponds to the length of the needle from its tip to a point 2 cm. from the indicator arrow (fig. 1).

A no. 7 Aorto-catheter, 53 cm. in length, may be used in identical fashion with the no. 19-gage transseptal needle used in infants.

*Manufactured by U. S. Catheter and Instrument Company, Glens Falls, New York.

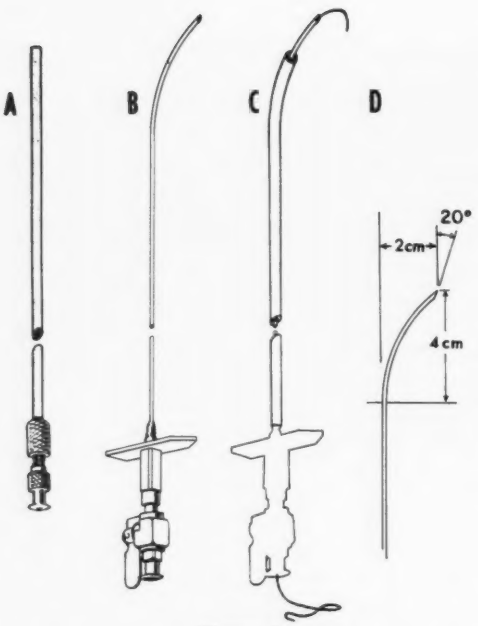

Figure 1

A. *Shortened no. 8 Aorto-catheter and removable adapter.* B. *Transseptal needle.* C. *The transseptal needle has been extended beyond the tip of the catheter and the polyethylene catheter has been passed through the needle.* D. *Scale drawing of the curved distal end of the needle.*

Transseptal Needles

The transseptal needle for routine use (fig. 1) is constructed of no. 17-gage thin-walled stainless-steel tubing and is approximately 61 cm. in length.* A stopcock is permanently attached to the proximal end and immediately distal to it is a metal arrow mounted so that it points in the same direction as the curvature of the distal end of the needle. The shape of the curve in the needle tip has been found to be important in facilitating septal puncture, and it is reproduced to scale in figure 1. The convex surface of the curve in the needle terminates in the leading edge of the needle point and the opening of the needle thus faces the concave surface. The margins of the opening are carefully polished to avoid shearing of the fine plastic catheter that is passed through it.

The transseptal needle employed for angiocardiography* with selective injection into the left atrium, is identical to that described above except for its distal end, which has been modified in order to prevent recoil during injection of contrast material. The tip of the needle is closed and 3 spirally placed side holes (.034", .032", and .030" in diameter, with the largest hole distally) are drilled in the terminal centimeter of the needle.

The needle employed for transseptal puncture in infants and young children is 55 cm. in length, and is constructed of no. 19-gage tubing.

Polyethylene Catheter

A polyethylene catheter 100 cm. in length (Clay-Adams PE 50) with an adapter (Clay-Adams A-2625) at its proximal end is passed through the no. 17-gage transseptal needle for catheterization of the left ventricle and aorta.

Technic of Transseptal Left Heart Catheterization

The patient is prepared by fasting and 100 mg. of pentobarbital are given by mouth 1 hour before the procedure. After local infiltration with 1 per cent Xylocaine, a transverse incision, 3 cm. in length, is made approximately 1 inch below the right inguinal ligament and medial to the pulsation of the femoral artery. With use of a small self-retaining retractor to aid exposure, the saphenous vein is isolated below its junction with the femoral vein. The saphenous vein is ligated distally, and a loose ligature is placed proximally to prevent bleeding from above. When the right saphenous vein has been ligated at a previous time, it is often possible to pass the catheter through the proximal segment or one of the major saphenous branches. If no patent vein can be found on the right, the left saphenous vein is then employed. When the approach is made from the left groin, passage of the catheter and needle sometimes results in abdominal or lower back pain due to traction on the inferior vena cava; this may be minimized by bending the trunk to the right in order to straighten the course of the catheter and needle.

Right heart catheterization is first carried out with a standard catheter. The use of a rotating adapter* between the cardiac catheter and the connecting tubing that leads to the pressure transducer facilitates upward rotation of the curved tip of the catheter from the right ventricular apex toward the outflow tract and pulmonary artery. Upon the completion of right heart catheterization the standard catheter is withdrawn.

Before performing transseptal left atrial puncture, the short no. 8 catheter is inspected. The adapter is removed and the transseptal needle is fully inserted. Unobstructed passage of the needle through the catheter is thus assured, and excessive protrusion of the needle tip beyond the recommended 2 cm. may be detected. Following removal of the needle, replacement of the adapter, and attachment of a stopcock, the catheter is inserted

*Manufactured by Becton-Dickinson Co., East Rutherford, New Jersey.

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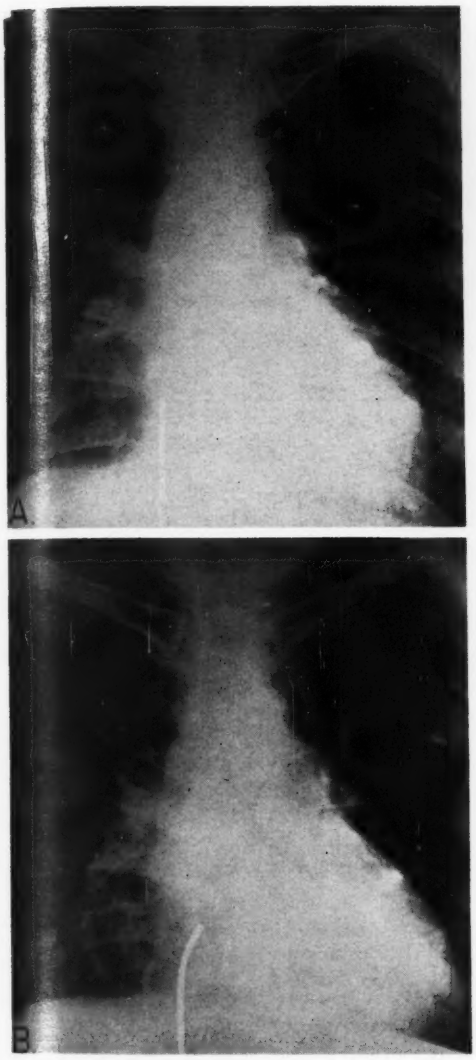

Figure 2

A. *Roentgenogram demonstrating the proper position of the catheter in the right atrium prior to insertion of the transseptal needle.* B. *The transseptal needle has been advanced so that its tip lies just within the cardiac catheter and the indicator arrow attached to the needle hub has been rotated posteromedially so that the catheter tip impinges on the interatrial septum.* C. *The needle has been advanced beyond the catheter tip, thereby puncturing the septum.*

into the vein and advanced so that its tip lies in the mid portion of the right atrium (fig. 2*A*). The adapter is then removed, and the transseptal needle is inserted and gradually advanced. As the needle approaches the junction of the saphenous and femoral veins the curvature is directed posteriorly. It is important to permit the needle to rotate within the lumen of the catheter as it is advanced beyond this area. Free rotation of the needle will occur as it is gently pushed upward. In order to avoid perforation of the wall of the catheter excessive force must not be employed when advancing the needle. If an obstruction to passage of the needle is encountered, it may often be circumvented by manipulating the catheter and needle together beyond the site of obstruction. The needle is advanced until its point lies just within the tip of the catheter in the right atrium. With the aid of the fluoroscope, the catheter tip is then positioned at the junction of the lower and middle thirds of the right atrial silhouette. With one finger placed on the point of the indicator at the proximal end of the needle, the catheter tip is directed posteromedially at an angle of approximately 45° from the horizontal plane (fig. 2*B*). In the presence of an enlarged left atrium the resistance offered by the bulging interatrial septum may often be felt upon completion of this maneuver. When this resistance is not encountered, alternately advancing and withdrawing the catheter will frequently result in contact with the atrial septum. The site chosen for puncture should be visualized fluoroscopically; in order to avoid the ascending aorta it should be within the lower half of the right atrial silhouette. The transseptal needle is now attached to a pressure transducer by means of a flexible connecting tube. With the catheter held stationary in one hand, and with the indicator arrow of the needle maintained at the 45° angle

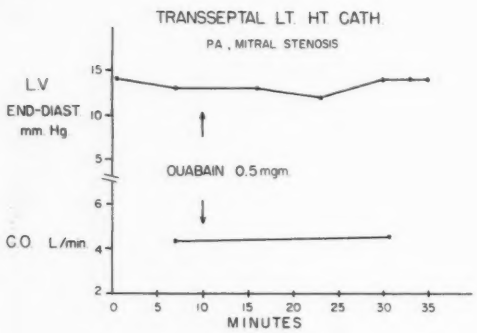

Figure 3

Left ventricular end-diastolic pressure and measurements of cardiac output obtained during the course of transseptal left heart catheterization in patient P. A. with rheumatic heart disease and mitral stenosis. Ouabain, 0.5 mg., was injected at the time indicated by the vertical arrows.

with the other hand, the needle is pushed forward the remaining 2 cm. A sudden decrease in resistance is usually appreciated as the needle perforates the septum and enters the left atrium (fig. 2*C*). The atrial pressure pulse is observed on the monitoring oscilloscope and identified as left atrial in origin by comparison with the previously observed right atrial pressure. In addition, the free withdrawal of oxygenated blood should be possible. Frequently, penetration of the septum is initially incomplete and a high, nonphasic pressure is observed. In this situation the puncture may be completed by advancing the protruded needle and catheter together, approximately 1 cm., until the septum is pierced.

After left atrial pressure has been recorded the polyethylene catheter is advanced through the transseptal needle into the left atrium. The pressure recorded from the tip of the catheter is monitored continuously on an oscilloscopic screen as the catheter is slowly advanced and withdrawn until left ventricular pressure is recorded. It is sometimes helpful to rotate the indicator arrow of the needle to a more horizontal or vertical position in order to modify the initial direction of the polyethylene catheter. Occasionally the catheter may also be manipulated from the left ventricle across the aortic valve into the aorta. When desired, the hemodynamic effects of exercise may be studied by means of a bicycle ergometer pedaled with one leg.

Upon completion of the procedure the polyethylene catheter is first withdrawn, then the needle is removed slowly with the catheter still in place. Finally, the Aorto-catheter is removed, and the saphenous vein is ligated.

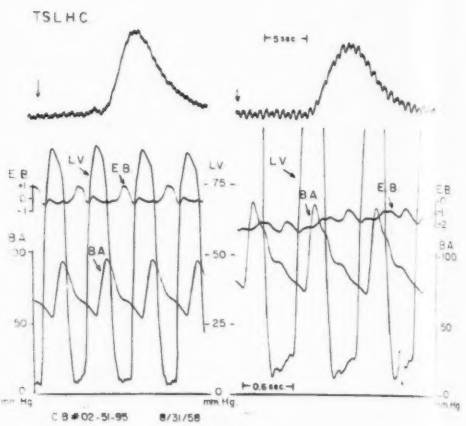

Figure 4

*Hemodynamic observations before (*left*) and after (*right*) the infusion of 1,500 ml. of whole blood into a human subject. The upper panels are dye-dilution curves for the measurement of cardiac output. On the lower panels the left ventricular (LV), brachial artery (BA), and intra-esophageal balloon (EB) pressure pulses are reproduced.*

Results

Transseptal left atrial puncture has been performed successfully in 130 patients at the National Heart Institute. There has been no death and no significant complication. Puncture of the free wall of either atrium or of any structure other than the atrial septum has not occurred to our knowledge in any instance. No intrapericardial bleeding has been evident clinically or at subsequent operation. Nitrous oxide tests for the detection of left-to-right shunts were performed before and after transseptal puncture in 10 patients and all tests were negative. The atrial septum could not be punctured in several patients, most of whom had gross enlargement of the right atrium. In these patients displacement of the inferior vena cava and septum prevented contact of the needle with the septal wall. In 2 patients whose hearts were studied at postmortem examination, 5 days and 4 weeks following atrial puncture, pinpoint holes covered by minute white thrombi were found in the region of the foramen ovale. Occasionally one or two atrial premature contractions may be observed at the time of transseptal puncture. No serious or prolonged

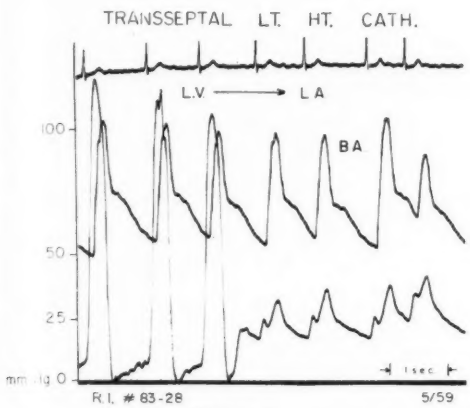

Figure 5

Tracing obtained as the polyethylene catheter was withdrawn from the left ventricle (LV) across the mitral valve into the left atrium (LA) in a patient with mitral stenosis.

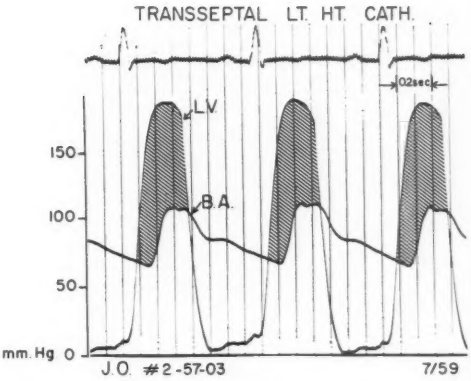

Figure 6

Pressure pulses recorded simultaneously from the left ventricle (LV) and brachial artery (BA) in a patient with congenital aortic stenosis. The shaded area represents the pressure gradient between these two sites.

arrhythmias have occurred, however. There has been little or no discomfort, although in a few instances the patients have reported a brief sensation of fullness in the mediastinum and neck during septal puncture.

In the early experience with transseptal left heart catheterization, left ventricular catheterization was not attempted systematically, but the left ventricle has been entered in 40 of the last 50 patients (80 per cent). Failure to catheterize the left ventricle has usually occurred in patients with gross mitral regurgitation. When it was deemed necessary, anterior percutaneous left ventricular puncture[7] was carried out and simultaneous left atrial and ventricular pressures were recorded. Difficulty in advancing the catheter freely within the left atrium occurred in several patients subsequently demonstrated at operation to have large thrombi within this chamber.

Applications of Transseptal Left Heart Catheterization

This method of left heart catheterization has been applied in two general areas of hemodynamic investigation. Increasing evidence of the safety of the transseptal approach has prompted its use in several physiologic and pharmacologic studies of the dynamics of the left side of the heart carried out in the course of catheterization. Since the patient experiences no discomfort, measurements of left heart pressures and cardiac output may be made over a long period of time with the patient in a steady and basal state. For example, the effect on left ventricular end-diastolic pressure and cardiac output of digitalization with a rapidly acting glycoside has been studied in a variety of patients (fig. 3). The applicability of Starling's law of the heart to the circulation of intact human subjects is also under investigation. The effects of acutely induced hypervolemia on effective ventricular end-diastolic pressure and cardiac output has permitted the construction of left ventricular function curves[16] in man (fig. 4). During studies of this type left ventricular pressure measurements have been carried out for periods in excess of 2 hours.

Transseptal left heart catheterization has been found equally useful in diagnostic studies and the availability of this technic has broadened the indications for diagnostic left heart catheterization. In patients with valvular heart disease the usual recordings of the left atrial pressure pulse and of the pressure gradient across both the mitral and aortic valves may be readily obtained both at rest and during exercise. Representative

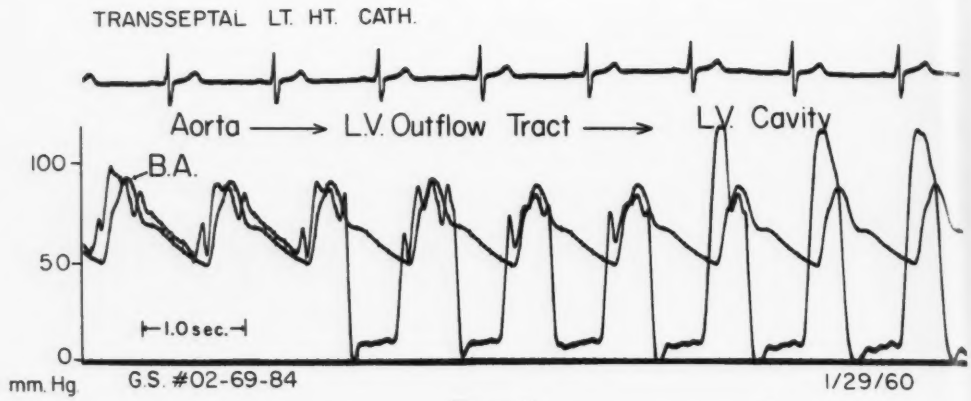

Figure 7

Pressure pulses recorded as the polyethylene catheter was withdrawn from the aorta across the aortic valve, through the left ventricular outflow tract and into the main cavity of the left ventricle (LV). There is a moderate pressure gradient between the main cavity of the left ventricle and the left ventricular outflow tract. BA refers to the simultaneously recorded brachial artery pressure pulse.

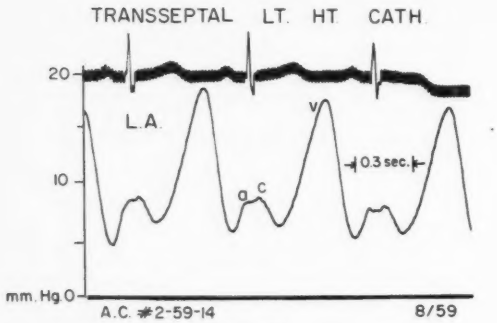

Figure 8

Pressure pulse recorded from the left atrium (LA) of a 2-year-old child with a ventricular septal defect and intact interatrial septum. The 19-gage transseptal needle was employed. The prominent "v" wave is related to increased filling of the left atrium during ventricular systole.

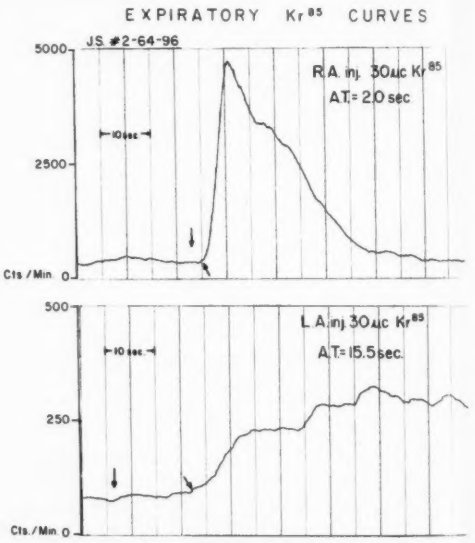

Figure 9

Concentration of Kr^{85} in expired air following injection into the right atrium (RA, top panel) and left atrium (LA, lower panel) in a patient without a circulatory shunt. A.T. represents appearance time. The vertical arrows indicate the instant of injection and the oblique arrows the appearance of the isotope in expired air.

tracings of this type are reproduced in figures 5 to 7. Measurements of cardiac output by the indicator-dilution technic with left heart injection are also conveniently performed in the course of these studies.

The transseptal route has been found to be particularly applicable for left heart catheterization in children. Experience so far indicates that the smaller size of the heart does not render the technic more difficult. General anesthesia has been required only in infants. The ease with which left heart catheterization may now be performed in children has permitted its use in the study of patients

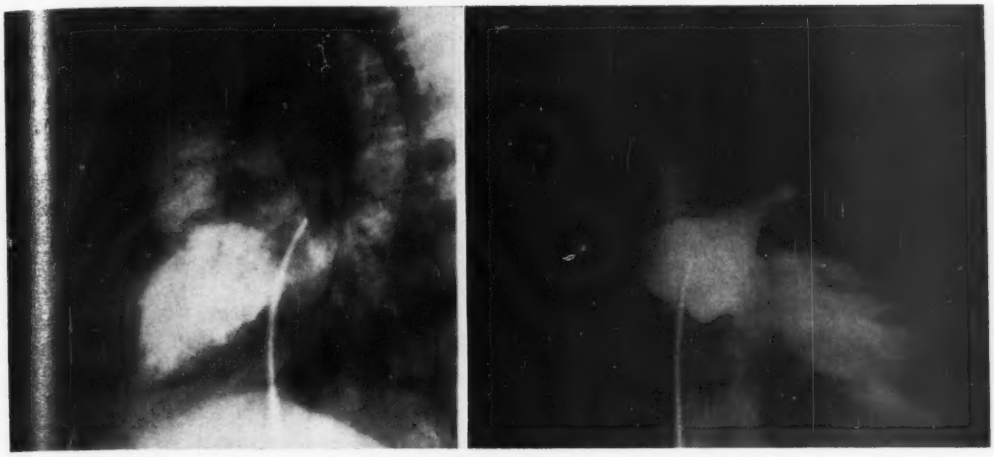

Figure 10

Selective angiocardiogram following left atrial injection in a patient with congenital aortic stenosis. The lateral projection is on the left and the anteroposterior projection on the right.

with congenital heart disease and intact atrial septa (fig. 8). Injections of indicator dye or of solutions of radioactive krypton into the left atrium and ventricle[17] have facilitated the localization of the site of origin of left-to-right shunts (fig. 9).

Recently, the transseptal technic has been extended to permit selective angiocardiography with left atrial injection. It is anticipated that this approach will be found increasingly useful when visualization of the detailed anatomy of the chambers and valves of the left side of the heart is required (fig. 10).

Comments

Although final evaluation of transseptal left heart catheterization must be reserved until a larger number of patients has been studied, the superiority of the method is suggested by the experience to date. Of greatest importance would seem to be its safety. The intravascular route of the needle avoids the hazards attendant upon external puncture; pneumothorax, hemothorax, cardiac tamponade, and unexplained hypotension have thus been obviated. It is conceivable, however, that improper use of the transseptal needle could result in puncture of the aorta, the free wall of the right atrium, or of the coronary sinus. It is important, therefore, that the operator be well acquainted with the detailed relation of these structures to the atrial septum; before the procedure was undertaken in this clinic it had been utilized extensively both in dogs[11] and in cadavers. Furthermore, the chest roentgenogram of each patient should be studied before catheterization in order that the position of the aorta, the size of the atria, and any anomalies of position or rotation of the heart be known. When these precautions are observed, the procedure is technically simple and can be performed by anyone trained in the usual right heart catheterization technics. The participation or immediate availability of a thoracic surgeon or endoscopist is therefore not mandatory.

Another advantage of transseptal left heart catheterization is the ease with which it may be combined with right heart catheterization; both procedures are performed through a single venous intubation. Furthermore, when the need for left heart catheterization or left atrial angiocardiography becomes apparent in the course of right heart studies, transseptal left atrial puncture may be performed forthwith. For this reason, the right saphenous vein is now used for right heart catheterization in many patients.

The procedure results in no more discomfort to the patient than an ordinary right heart catheterization and in this respect is clearly preferable to the posterior percutaneous and transbronchial methods of left atrial puncture. The disadvantages of the latter technic in the study of children are well recognized[9] and transseptal left heart catheterization is certainly the method of choice in this age group. Its increasing use in patients with congenital heart disease is anticipated.

Finally, it appears that catheterization of the left ventricle with the fine polyethylene catheter passed through the transseptal needle is accomplished as readily as with other methods of left atrial puncture. When the left ventricle cannot be entered, the supine position readily permits anterior percutaneous puncture of the left ventricle, a procedure not easily accomplished with the patient in the prone position required for posterior percutaneous left atrial puncture.

Summary

Experiences with left heart catheterization by the transseptal route in 130 patients are presented. The instruments and technics employed are described in detail and some of the applications in diagnosis and clinical investigation of the method are illustrated. The advantages of transseptal left heart catheterization, which indicate its superiority over other technics, are discussed.

Summario in Interlingua

Es presentate experientias in catheterismo sinistro-cardiac a accesso transseptal in 130 patientes. Le instrumentos e le technicas usate es describite in detalio, e certes del applicationes in le diagnostica e le investigation clinic es illustrate. Le avantages es discutite que inhere in transseptal catheterismo sinistro-cardiac in comparation con altere technicas.

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Treatment of Shock and Prevention of Ischemic Necrosis with Levarterenol-Phentolamine Mixtures

By GARY ZUCKER, M.D., ROBERT P. EISINGER, M.D., MARTIN H. FLOCH, M.D., AND MARK M. SINGER, M.D.

ISCHEMIC NECROSIS resulting from accidental extravasation of levarterenol (Levophed) in patients in shock can be prevented by local injection of 5 or 10 mg. of the anti-adrenergic drug phentolamine (Regitine).[1-4] This method is not effective when vasoconstriction has existed for several hours and irreversible tissue damage has occurred.

Preliminary observations suggest that immediate protection can be secured by adding phentolamine to the flask of levarterenol.[5, 6] In rabbits, as little as 2.5 mg./L. of phentolamine antagonizes the necrotizing effect of solutions containing 8, 16, and 32 mg./L. of levarterenol.[5] In 5 normotensive patients, 5 to 40 mg./L. of phentolamine did not diminish the pressor effect of levarterenol. Similar observations were made in 5 patients in shock.[6]

The purpose of this paper is to evaluate the routine use of levarterenol-phentolamine mixtures in treatment of 68 cases of shock.

Material and Methods

Of the 68 cases, shock was due to coronary thrombosis in 25, terminal malignancy in 12, operative procedure in 9, sepsis in 6, pulmonary embolism in 4, cerebral hemorrhage or thrombosis in 4, hepatic coma in 2, aortic rupture in 1, and arrhythmia in 1. The patients had a systolic pressure of 80 mm. Hg or less and clinical signs of shock, such as pallor, sweating, cyanosis, restlessness, torpor, and oliguria.

Mixtures were prepared in 1,000 ml. of 5 per cent glucose in water and administered by needle or polyethylene catheter into a vein of the forearm, antecubital fossa, hand, or leg.

Vasopressor treatment was started with a mixture containing 4 or 8 mg./L. of levarterenol. Rate of administration was at or below 20 drops per minute. Increments of 4 mg. of levarterenol were added when needed to maintain elevation of blood pressure.

The concentration of phentolamine varied at different stages. At first, 5 to 10 mg. were added for each 4 mg. of levarterenol. Subsequently, regardless of levarterenol dosage, 10 mg. and later only 5 mg. of phentolamine were added to each liter.

Extravasations were observed but no local therapy was administered.

Results

Continuous vasopressor therapy was administered for 1 hour to 11 days. The dosage of levarterenol was 4 to 48 mg./L. and of phentolamine 5 to 60 mg./L. or a range of 0.08 to 0.96 mcg./Kg./minute for levarterenol and 0.1 to 1.2 mcg./Kg./minute for phentolamine. Good pressor responses were obtained in 51 cases (75 per cent), as evidenced by a systolic blood pressure of 90 to 120 mm. Hg. Twenty patients survived shock and maintained normal blood pressure after vasopressor therapy was discontinued: 9 cases of coronary thrombosis (36 per cent), 7 cases of postoperative shock (78 per cent), 1 case of sepsis, (16 per cent), 1 case of pulmonary embolus (25 per cent), 1 case of cerebral thrombosis (25 per cent), and in the only case of cardiac arrhythmia. No recovery was observed in any case requiring more than 20 mg./L. of levarterenol. Survivals from shock were observed with mixtures containing 5 to 50 mg./L. of phentolamine.

Thirty-four extravasations occurred in 22 patients (fig. 1). None of the mixtures produced any necrosis. The only patient who developed a slough was of crucial interest, since he served as his own control. He had two large extravasations of mixtures involving both arms and antecubital fossae, which did not produce any necrosis. One contained 8 mg./L. and the other 12 mg./L. of levarterenol; both contained 10 mg./L. of phentolamine. He also had a smaller extravasation of 8 mg./L. of levarterenol on the leg, from which phentolamine had inadvertently been

From the Department of Medicine, Beth Israel Hospital, New York, N. Y.

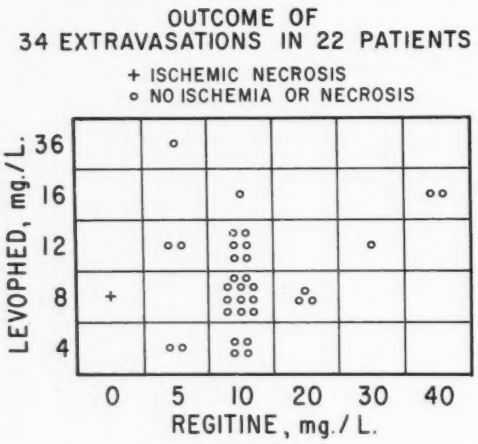

Figure 1

Absence of necrosis in extravasations of levarterenol-phentolamine mixtures.

omitted; a large slough developed within 72 hours. All infiltrations occurred in spite of cut-downs and polyethylene catheters.

Discussion

Phentolamine can be given together with levarterenol by slow intravenous drip to patients in shock without reducing pressor response. This fact is attributable to the low rate of administration. For the average adult receiving 5 or 10 ml./L. of phentolamine this would be equivalent to 0.1 to 0.2 mcg./Kg./minute. This is much less than that previously used for antihypertensive effect; Moyer and Caplovitz[7] gave 1 to 3 mg./Kg. as a single intravenous injection. The local tissue concentration of phentolamine, however, is high enough in areas of extravasation to prevent vasoconstriction and necrosis. Despite slight dilution by extracellular fluid it approximates the concentration in the flask. No necrosis ensued in 22 instances in which 10 mg./L. of phentolamine were used and in 5 extravasations in which 5 mg./L. of phentolamine were used (fig. 1). It is our current practice to administer mixtures containing only 5 mg./L. of phento'amine. Only in this manner can enough experience be accumulated to determine whether this is the smallest effective dose.

The heterogeneous nature of the group, which included different types of shock and many patients with terminal diseases precludes a definitive evaluation of the effect of the mixtures upon prognosis. On the other hand the 25 cases of coronary thrombosis are a homogeneous group and represent a prime indication for vasopressor therapy. Nine cases (36 per cent) recovered from shock, a result comparable to those obtained with levarterenol alone.[8, 9]

Levarterenol has certain advantages over other pressor amines. These include the rapid onset and offset of action, the ease with which dosage can be varied, and its efficacy in some cases in which other vasopressor drugs have failed. Its tendency to produce ischemic necrosis at sites of extravasation has discouraged its use. Routine addition of 5 or 10 mg. of phentolamine may eliminate this one serious disadvantage. The method is simple, pressor response is not diminished, and protection against local ischemia is automatic.

Summary

Good pressor responses were obtained in 51 of 68 cases of shock treated with levarterenol-phentolamine mixtures. No necrosis developed in 33 extravasations of mixtures. One slough resulted from an extravasation of 8 mg./L. of levarterenol alone. Our present practice is to add 5 mg. of phentolamine to each liter of levarterenol solution.

Summario in Interlingua

Bon responsas pressori esseva effectuate in 51 ex 68 casos de choc tractate con mixturas de levarterenol e phentolamina. Nulle necrosis se disveloppava in 33 occurrentias de extravasation del mixtura, sed un tal esseva notate in le caso de un extravasation de 8 mg/L de levarterenol sol (ab que le admixtion de phentolamina habeva essite omittite accidentalmente). Currentemente nostre practica es adder 5 mg de phentolamina a omne litro de solution de levarterenol.

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One of the fine traditions of the practice of medicine, which may be giving shelter to something quite unsatisfactory, is the tradition of charity. Charity, like a loving mother, may override the rights of others in the protective solicitude, not to say the selflessly selfish ambition, she has for her own. Operating as charities, the hospitals have accepted or demanded, in the name of charity, the services of nurses, interns, and even patients in ways and to a degree that raise, at least retrospectively, questions as to who was giving what and in whose name. The time and care that nurses and interns have given hospital patients were required in the name of education and dispensed in the name of charity. Patients were called charity cases, but if they were used for teaching, it was not so often explained to them that this improved their care as that it was justified as a substitute for hospital fees. Doctors, for all that hospital positions enlarged their experience and enhanced their professional prestige, gave an enormous amount of time and effort in the name of charity. Even universities were expected to contribute to the care of the sick poor, which was charity though usually charged and considered as education.—ALAN GREGG, M.D. *Challenges to Contemporary Medicine.* New York, Columbia University Press, 1956, p. 86.

Pulmonary Vascular Resistance after Repair of Atrial Septal Defects in Patients with Pulmonary Hypertension

By WALTER BECK, M.D., H. J. C. SWAN, M.B., HOWARD B. BURCHELL, M.D., AND JOHN W. KIRKLIN, M.D.

THE BEHAVIOR of the pulmonary vascular bed in congenital heart disease is a topic of major current interest.[1-3] The control of normal pulmonary vessels remains a matter for debate, in part because of difficulty in measurements and in the interpretation of the small differences in pressure across the normal pulmonary vascular bed. In the presence of pulmonary hypertension, however, the responses of the pulmonary vessels may be assessed with greater certainty, since sizable pressure gradients frequently exist.

Although a pulmonary arterial systolic pressure in excess of 30 mm. Hg is outside the normal range in this laboratory, the categorization of all patients with septal defects and pressures above this level as having pulmonary hypertension is of questionable value. Accordingly, we have adopted a pulmonary arterial systolic pressure of 60 mm. Hg as the most suitable compromise above which patients may be said to have significant pulmonary hypertension. Such a division serves to separate most patients with congenital heart disease in whom increased pulmonary arterial pressure contributes significantly to the total problem from those in whom it does not. Classification on the basis of pulmonary vascular resistance remains the most important conceptual differentiation but suffers from the use of values that are indirect and open to far greater error than is the simple measurement of pulmonary arterial pressure.

In atrial septal defects associated with pulmonary hypertension as just defined, the pulmonary vascular resistance usually is increased. That this results in part from vasoconstriction may be concluded from the response to the inhalation of 100 per cent oxygen[4] and the infusion of acetylcholine[5] when both pressure and flow are measured. The stimulus for this vasoconstriction is not known, but the level of pressure within the pulmonary artery may be a factor in determining the level of vascular tone,[1] as it is for the systemic circulation.[6, 7]

A group of 11 patients with atrial septal defects and pulmonary arterial systolic pressure in excess of 60 mm. Hg was studied hemodynamically before and after closure of the defects. The data were reviewed with the primary purpose of determining whether the changes in pulmonary arterial pressure could be related to changes in pulmonary vascular resistance.

This study also afforded an appraisal of the physiologic response to surgical closure of intra-atrial defects in patients with complicating pulmonary hypertension. Such patients present a special problem in selection for surgical treatment. The assessment of their operability based on criteria previously described[8] for ventricular septal defect can be difficult at times. In some of these patients, a return to normality after repair of the defect is prevented by the persistence of pulmonary hypertension caused by pulmonary vascular disease. The response of increased pulmonary vascular resistance to repair of the defect then becomes of great practical as well as theoretic importance. Furthermore, the general conclusions drawn from a study of patients following repair of atrial septal defects may possibly be transferred to patients with pulmonary hypertension complicating other defects.

Our studies indicate that pulmonary vascular resistance may be reduced markedly in

From the Mayo Clinic and the Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

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some patients with atrial septal defects. We are aware of the difficulties in the interpretation of calculated vascular resistance; nevertheless, the data support the concept that pulmonary arterial pressure may indeed play a part in the regulation of tone in the pulmonary vascular bed in some patients.

Material and Methods

Eleven patients with atrial septal defects, including 3 men and 8 women ranging in age from 25 to 51 years, all of whom had pulmonary arterial systolic pressures in excess of 60 mm. Hg, were studied at intervals of 3 to 34 months after closure of the defects. All defects were repaired by the atrial-well technic of Gross,[9] as modified by Kirklin and associates.[10] All patients were studied preoperatively in this laboratory by the cardiac-catheterization technic previously described.[11] At this time, pulmonary and systemic blood flows were determined by the Fick method. Pulmonary pressures were measured and resistances were calculated according to standard formulas.[12] In 9 instances, the observations were repeated while the patients breathed oxygen.[4]

At the postoperative study, all 11 patients were found to have had complete repair of the defect. Pulmonary arterial pressures and pulmonary arterial "wedge" pressures (9 patients) were obtained, and the pulmonary blood flow was measured by the Fick method and in 1 case also by the indicator-dilution technic,[13] with indocyanine green as the indicator. The dilution curves were recorded by means of a cuvette oximeter that was calibrated in terms of response to the concentration of dye after the study. The response to exercise in the supine position with an "exercycle" was determined as previously described.[14] Attempts were made to obtain more than one level of pulmonary arterial pressure in 2 patients by changing the speed at which the exercycle was rotated, thus varying the level of work.

Results

Preoperative Hemodynamic Status

The ratio of pulmonary to systemic blood flow was less than 1.75 in 7 of the 11 patients (table 1). The pulmonary vascular resistance exceeded 600 dynes seconds cm.$^{-5}$ in 5 patients.

Change in Basic Dynamics after Closure of Defect

Mean systolic and diastolic pulmonary arterial pressure decreased significantly in all instances except in case 2 (table 1). The average

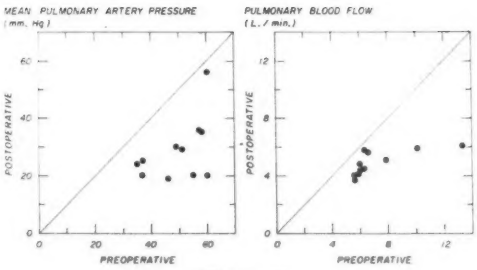

Figure 1

Change in mean pulmonary arterial pressure and pulmonary blood flow after closure of atrial septal defects in 11 patients with pulmonary hypertension. Points below the diagonal line indicate a reduction. Note that significant reduction in pressure and flow occurred in most instances. The patients with the greater flows tended to have the lower mean pulmonary arterial pressures (table 1).

mean pulmonary arterial pressure was 49 mm. Hg before closure of the defect and 29 mm. after closure. Likewise, the pulmonary blood flow declined in every instance from an average of 7.9 to 4.9 liters per minute (fig. 1).

Direct measurements of left atrial pressure were not obtained uniformly before operation. The relationship of mean pulmonary arterial wedge pressure (postoperative) to mean right atrial pressure (preoperative) suggests an increase in mean left atrial pressure after operation (fig. 2). In 3 patients, wedge pressure was obtained at the preoperative study, and it exceeded the right atrial pressure by 2 to 4 mm. Hg.

Among the patients with increased resistance, excepting case 2, the total pulmonary resistance declined from an average of 620 dynes seconds cm.$^{-5}$ before repair to 440 dynes seconds cm.$^{-5}$ after operation, while the pulmonary vascular resistance declined to a greater extent, the average values for the latter being 510 before operation and 230 after repair (fig. 3).

Response to Breathing 100 Per Cent Oxygen

In the preoperative study, the effect of breathing 100 per cent oxygen was determined in 9 of the 11 patients, as already noted. Seven of these 9 patients showed a significant decrease in pulmonary vascular re-

Table 1

Pulmonary Pressure, Flow, and Resistance before and after Closure of Atrial Septal Defects with Significant Pulmonary Hypertension†*

Case	Age, yr.	Sex	Body surface area, M^2	O_2 consumption, ml./min./M^2	Pressure, mm. Hg: PA Sys./dias.	PA Mean	PAW, mean	RA, mean	SA, sys./dias.	Pulmonary blood flow, L./min. (Q_p)	$Q_p : Q_s$, precop.	Resistance, dynes sec. cm.$^{-5}$: R_p	R_{pv}	R_s	Time postop., months
1	46	F	1.60	105	109/36	60	—	9	120/64	6.0	1.94	800	680	2140	22
			1.64	106	30/15	20	14	—	140/75	4.8		330	100	1630	
2	27	F	1.48	126	94/43	60	—	3	107/64	6.0	1.13	800	760	1180	3
			1.47	130	83/43	56	9	—	108/73	4.4		1010	850	1550	
3	48	F	1.51	128	100/37	58	—	6	119/51	5.9	1.6	790	700	1680	11
			1.54	125	50/27	35	—	—	119/49	4.1		680	—	1400	
4	31	F	1.67	140	91/41	57	—	6	125/76	6.3	1.61	720	650	1800	10
			1.67	134	52/28	36	18	—	110/70	5.9		490	240	890	
5	51	F	1.48	132	102/31	55	—	5	141/76	5.6	1.65	790	710	2300	23
			1.63	118	32/14	20	9	—	164/89	4.0		400	220	2280	
6	25	F	1.66	140	68/43	51	9	5	111/66	10.1	1.92	400	360	1220	22
			1.69	130	41/22	29	11	—	115/64	5.9		390	240	1100	
7	32	F	1.67	141	78/35	49	11	7	118/76	7.9	1.15	500	420	970	12
			1.61	120	43/23	30	9	—	105/65	5.1		470	330	1225	
8	45	M	1.76	160	82/28	46	—	4	112/66	13.4	3.26	270	250	1550	34
			1.78	183	25/14	19	12	—	134/76	6.0		250	90	1270	
9	32	M	1.91	127	66/22	37	—	8	110/60	12.1	3.1	240	190	1470	3
			1.89	145	48/19	25	—	—	109/53	6.1		330	—	940	
10	46	F	1.60	118	66/22	37	7	5	103/58	5.6	1.6	530	460	1670	5
			1.62	131	35/12	20	8	—	113/55	3.7		430	260	1580	
11	44	M	1.85	134	65/20	35	—	5	120/72	6.3	1.61	445	380	1810	11
			1.88	128	36/18	24	12	—	109/61	4.5		430	210	1365	

*The upper value of the pairs is that before operation, and the lower one is that after operation.

†PA, pulmonary artery; PAW, pulmonary arterial wedge; RA, right atrium; SA, systemic artery; Q_p, pulmonary flow; Q_s, systemic flow; R_p, total pulmonary resistance; R_{pv}, pulmonary vascular resistance; R_s, systemic resistance.

sistance while breathing oxygen; this decrease averaged 40 per cent of the control level. One patient showed no change and another exhibited possibly a slight increase in resistance. The relationship of the change in resistance after closure of the defect to the change caused by breathing oxygen is shown in figure 4. With one exception, patients who had the greatest reduction in vascular resistance while breathing oxygen preoperatively tended to have the largest decrease after closure of the defect.

Response to Exercise after Closure of Defects

The changes in mean pulmonary arterial pressure, pulmonary arterial wedge pressure and pulmonary blood flow induced by exercise are shown in table 2. Patients 7 and 8 were studied under 2 and 3 different levels of exercise, respectively. The level of exercise used in every patient caused nearly a 3-fold increase in the consumption of oxygen. During exercise, both pulmonary arterial pressure and pulmonary blood flow increased (fig. 5). That the increase in pressure is much greater than the increase in flow is shown by comparing the change in flow with the change in mean pulmonary arterial pressure and with the difference in pressure between the pulmonary artery and the left atrium (fig. 6). For patients who increase their pulmonary flow by a factor greater than 50 per cent, there appears to be a considerable increase in both the mean pulmonary arterial pressure and the difference in pressure between the pulmonary artery and the pulmonary arterial wedge. The values translated into total pul-

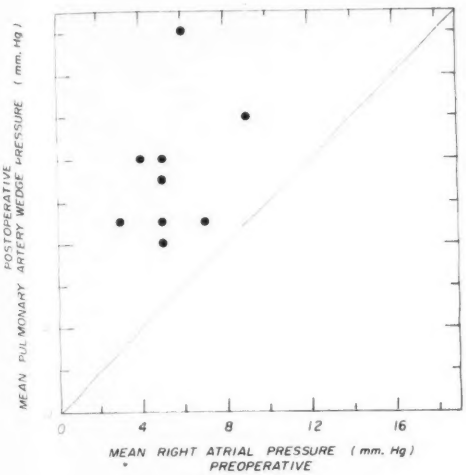

Figure 2

Change in "left atrial" pressure after closure of atrial septal defects. In all cases, the mean postoperative pulmonary arterial wedge pressure exceeded the preoperative mean right atrial pressure, the average difference being 6 mm. Hg.

monary resistance and pulmonary vascular resistance are shown in figure 7, in which increases in total pulmonary resistance and pulmonary vascular resistance of 27 and 60 per cent, respectively, were obtained.

Discussion

The patients in this study had atrial septal defects with a significant increase in pulmonary arterial pressure and with pulmonary blood flows that were in excess of systemic blood flows. After accepting the hazard of operation and surviving it, with complete closure of the defects, they returned for reevaluation by cardiac catheterization not less than 3 months after closure.

As anticipated, the physiologic responses of the pulmonary vasculature differed widely among these patients, since the factors initiating and accelerating pulmonary vascular changes probably are varied. In 1 patient (case 2), a 27-year-old woman who was studied 3 months after operation, the pulmonary arterial pressure remained virtually unchanged. At a similar pressure, a lesser quantity of blood was being driven through the

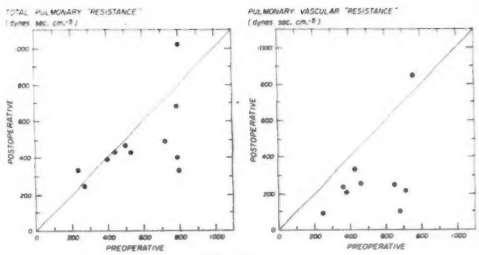

Figure 3

Change in ratio between pulmonary pressure and flow ("resistance") after closure of atrial septal defects. Note the reduction in total pulmonary "resistance" and, with one exception, an even greater reduction in pulmonary vascular "resistance." This occurred even in patients with severely increased vascular resistance (more than 600 dynes seconds cm.⁻⁵).

pulmonary vessels. This patient showed perhaps a slight increase in pulmonary vascular resistance. In the remaining patients, however, the decrease in pulmonary blood flow was proportionately less than the decrease in both mean pulmonary arterial pressure and the difference between pulmonary arterial and left atrial pressures.

Conclusions regarding the behavior of the pulmonary vascular bed in these patients depend largely on the interpretation of changes in the so-called pulmonary vascular resistance. Knowledge of calculated vascular resistance is one of the few variables for deciding on the status of the pulmonary vascular bed. For an individual patient, on the assumption that the viscosity of the blood and characteristics of the flow are not significantly different, an increase in pressure required to drive a given quantity of blood through the pulmonary vascular bed suggests that the geometric structure of the bed in some way has been narrowed. If a lesser head of pressure is required to deliver the same quantity of blood through a bed, it appears that the caliber of the bed has widened. The difficulties and dangers of such assumptions have been discussed extensively.[15, 16]

In 10 of our 11 patients, the mean pulmonary arterial pressure decreased significantly, and this measurement is not subject to any

Table 2

Effect of Exercise on Pulmonary Hemodynamics in Six Patients after Closure of Atrial Septal Defects

Case	Status	O_2 consumption, ml./min./M.^{2}	Pressure, mm. Hg $\bar{P}_{pa}$	Pressure, mm. Hg $\bar{P}_{paw}$	Pulmonary blood flow, L./min.	Resistance, dynes sec. cm.$^{-5}$ R_p	Resistance, dynes sec. cm.$^{-5}$ R_{pv}
1	Rest	106	20	14	4.8	330	100
	Exercise	514	56	28	9.7	460	230
4	Rest	134	36	18	7.2*	400	200
	Exercise	—	72	32	9.6*	600	330
5	Rest	118	20	9	4.0	400	220
	Exercise	427	52	—	7.1	590	—
7	Rest	120	30	9	5.1	470	330
	Exercise 1	304	39	8	6.9	450	360
	Rest	—	33	—	—	—	—
	Exercise 2	380	43	9	7.8	440	370
8	Rest	183	19	12	6.0	250	90
	Exercise 1	400	29	20	8.0	300	90
	Rest	—	21	11	—	—	—
	Exercise 2	632	42	19	8.3	400	220
	Exercise 3	308	27	—	6.5	330	—
11	Rest	128	24	12	4.5	430	210
	Exercise	360	37	17	6.5	450	250

*Cardiac output determined by indicator-dilution technic.

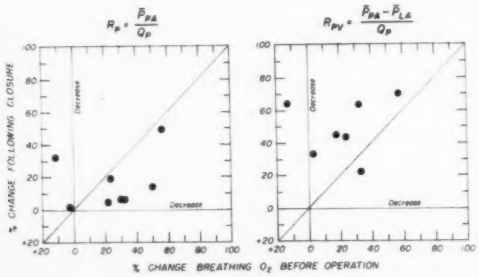

Figure 4

Relationship of the percentage change in pulmonary resistance associated with the breathing of oxygen before operation to the change after surgical closure of atrial septal defects in 8 patients. With the exception of case 4, a rough correlation was present between the decrease in resistance while oxygen was breathed preoperatively and the postoperative decrease in resistance.

important error. The magnitude of the pulmonary blood flow in all instances also declined. On some occasions, this decrease was equal in magnitude to the change of pressure, but more frequently it was much less than the change in pressure. Therefore, resistance either has not changed or has decreased (fig. 3). It follows that the vessels producing the resistance either have not changed in caliber or have dilated. As Burton and Yamada[17] have pointed out, the pressure that determines the size of the resistance vessels of a certain distensibility and vasomotor tone is the transmural pressure. In these patients, it can be assumed that the transmural pressure varied directly with the intravascular pressure, since there is no reason to suspect the presence of a significant postoperative change in extravascular pressure.

The intravascular pressure in the resistance vessel is affected by both the perfusion pressure (mean pulmonary arterial pressure) and the outflow pressure (mean left atrial pressure). Our data indicate a considerable decline in the perfusion pressure but possibly an increase in outflow pressure. A definite increase in left atrial pressure was demonstrated clearly in cases 1 and 4. In the remainder, the apparent increase in the postoperative wedge pressure over the preoperative right atrial pressure by an average of 5 mm. Hg might suggest a true increase in pulmonary venous pressure. However, a difference of similar magnitude was noted preoperatively in cases 6, 7, and 10 and in a bigger group of patients in whom large atrial defects were found.[18] A decrease in arterial pressure tends to diminish transmural pressure in the precapillary segment, and an in-

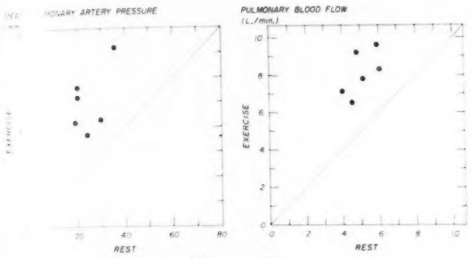

Figure 5

Changes in mean pulmonary arterial pressure and blood flow during exercise after closure of atrial septal defects. Note the significant increases in both pressure and flow.

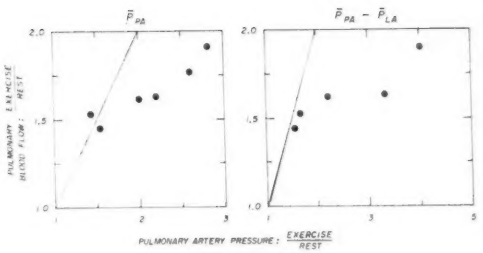

Figure 6

Relationship of the change in pulmonary blood flow to the change in pulmonary pressure during exercise after closure of atrial septal defects. The line of identity for proportionate changes in pressure and flow is indicated. When the ratio of the increase in flow exceeded 1.5, the increase in both the mean pulmonary arterial pressure and the difference in the pulmonary arterial and left atrial pressures was much greater than the increase in flow.

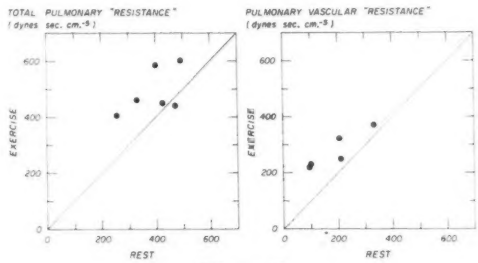

Figure 7

Change in ratio of mean pulmonary arterial pressure to pulmonary blood flow ("resistance") during exercise after closure of atrial septal defects. Note the tendency for resistance to increase or remain unchanged.

crease in left atrial pressure would tend to increase it in the posteapillary segment. In the normal pulmonary vascular bed, in which the capillaries, venules and veins may be of an importance that is equal to or greater than that of the arterioles in determining resistance to flow and probably have widely differing distensibilities, one would have difficulty in determining whether a change in resistance could be caused by a change in pulmonary venous transmural pressure.

In these patients, however, as in the great majority of those with congenital heart disease and pulmonary hypertension, much evidence of both hemodynamic and histologic nature indicates that most of the resistance to flow resides in a particular set of vessels, namely the arterioles and small muscular arteries. The average pressure in these vessels will be approximately midway between pulmonary arterial and pulmonary venous pressures, and by far the greater part of the total decrease in pressure to left ventricular diastolic levels takes place across them. From the data, it is seen that the average intravascular pressure at the level of the arterioles decreased in all our cases, and the change in left atrial pressure makes no difference in this conclusion. The values for resistance, however, indicate that the caliber of the vessels is unchanged or perhaps increased. The only explanation that appears possible is that the tone in the walls of the pulmonary vessels declined or that organic changes in these vessels resolved.

That vasomotor tone may play a part in this process can be concluded from the comparison of pulmonary vascular resistance at rest and during exercise in the postoperative studies. Exercise produced a considerable increase in mean pulmonary arterial pressure and a slight to considerable increase in left atrial pressure. Both precapillary and postcapillary transmural pressure increased. It appears that the resistance during exercise either remains unchanged or, more frequently, increases slightly. The vessels, therefore, are not dilating and may even be constricting despite an increased transmural pressure. This could be caused by structural changes in

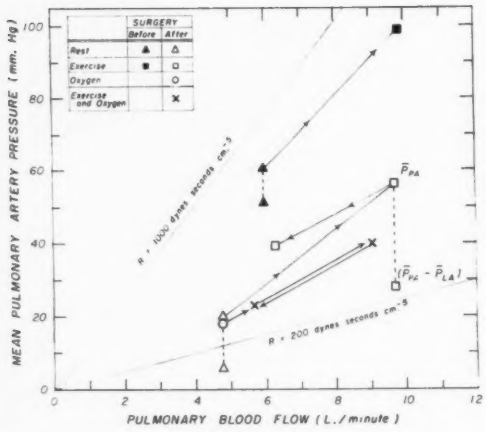

Figure 8

Relationship of pulmonary arterial pressure to pulmonary blood flow in a patient with atrial septal defect under varying conditions. Isoresistance lines, the upper representing 1,000 dynes seconds cm.$^{-5}$ and the lower 200 dynes seconds cm.$^{-5}$, are indicated. The solid symbols are the values obtained before operation, and the values joined by vertical dotted lines are the mean pulmonary arterial pressure and the difference between pulmonary arterial and left atrial pressures. During preoperative exercise, both pressure and flow increased proportionately; therefore, resistance remained unchanged. The open symbols are the postoperative values. At rest, values for pressure and flow were normal; during exercise, mean pulmonary arterial pressure and the difference between pulmonary arterial and left atrial pressures tended to increase proportionately more than did flow, so that resistance was slightly increased. The open circle and the crosses represent the values obtained while the patient breathed 100 per cent oxygen postoperatively. The resting values did not change; during exercise, however, for a similar increase in blood flow, the pressure increased to a lesser degree than it did when the patient breathed air. Note that for a pulmonary blood flow of 10 liters per minute during exercise the mean pulmonary arterial pressure was 100 mm. Hg before operation and only 55 mm. after operation.

the vessel walls that prevent their distention or by an increased vasomotor tone that would tend to balance the increased transmural pressure without permitting vascular distention.

The facts that the pulmonary vascular resistance in cases 1 and 4 increased by 130 and 65 per cent, respectively, during exercise and that this increase in resistance in case 1 was reduced by breathing 100 per cent oxygen, which apparently is a dilator of pulmonary vessels (fig. 8), suggest that an increased vascular tone is present during exercise. All these observations are in keeping with the hypothesis that the level of vasomotor tone in patients who have pulmonary hypertension associated with atrial septal defects varies inversely with the intrapulmonary pressure.[1]

The problem of the resolution of pulmonary vascular changes is uncertain. Three patients (cases 1, 4, and 5) showed extreme reduction in pulmonary vascular resistance. One of these (case 4) showed no significant reduction in vascular resistance preoperatively when breathing oxygen or when acetylcholine was used as a vasodilator; however, a dramatic decrease in resistance was noted 10 months after operation. This suggests that organic vascular disease may have resolved to some extent at least. In the other cases, the changes could be explained entirely on the basis of a reduction in vasomotor tone.

Summary and Conclusions

Eleven patients with pulmonary arterial systolic pressures in excess of 60 mm. Hg were studied before and 3 to 34 months after closure of atrial septal defects. Significant postoperative reduction in mean pulmonary arterial pressure and pulmonary blood flow occurred, averaging 21 mm. Hg and 3 liters per minute, respectively. In the 9 patients in whom it was measured, the pulmonary arterial wedge pressure exceeded the preoperative right atrial pressure by an average of 6 mm. Hg, with a range of 2 to 12.

The pulmonary vascular resistance increased after operation in 1 patient from 760 to 850 dynes seconds cm.$^{-5}$ In the 3 patients who had preoperative pulmonary vascular resistances of more than 600 dynes seconds cm.$^{-5}$, together with postoperative studies, it decreased by an average of 72 per cent; in 5 patients, who had preoperative values ranging from 190 to 460 dynes seconds cm.$^{-5}$, the average decrease was 26 per cent. Postoperative

measurements of wedge pressure were not obtained in the remaining 2 patients. The reduction in vascular resistance apparently is caused by reduction in vasomotor tone or regression of organic obstructive changes or both.

During moderate exercise, which caused a 3-fold increase in the consumption of oxygen, the average increase in pulmonary blood flow was 54 per cent and that in pressure was 99 per cent.

With the patients at rest, therefore, the hemodynamic findings are often within normal limits, but exercise produces an abnormal increase in pressure, so that the calculated resistance is increased or remains unchanged. This may be the result of increased vasomotor tone.

The findings in this study are consistent with the view that the level of pressure within the pulmonary artery is a factor regulating the degree of vasomotor tone in these abnormal vessels.

Summario in Interlingua

Dece-un patientes con systolic tensiones pulmono-arterial de plus que 60 mm de Hg esseva studiate ante e 3 e 34 menses post le clausion de defectos atrio-septal. Esseva constatate le occurrentia post-operatori de significative reductiones del tension pulmono-arterial medie e del fluxo de sanguine pulmonar medie. Le valores medie de iste reductiones esseva 21 mm de Hg e 3 litros per minuta, respectivemente. In le 9 patientes in qui le cuneate pression pulmono-arterial esseva mesurate, illo excedeva le tension dextero-atrial pre-operatori per un valor medie de 6 mm de Hg, con extremos de 2 e 12.

Le resistentia pulmono-vascular montava in 1 patiente ab 760 a 850 dynas-secundas-cm.$^{-5}$ In le 3 patientes in qui le resistentia pulmono-vascular pre-operatori esseva plus que 600 dynas-secundas-cm^{-5} e in qui studios post-operatori esseva effectuate, ille resistentia decresceva al media per 72 pro cento. In 5 patientes con valores pre-operatori de inter 190 e 460 dynas-secundas-cm^{-5}, le reduction medie amontava a 26 pro cento. In le remanente 2 patientes, nulle studio post-operatori esseva effectuate. Le reduction del resistentia vascular es causate apparentemente per le reduction del tono vasomotori o per un regression de organic alterationes obstructive o per ambe iste factores.

In exercitio de grados moderate, causante un triplice augmento in le consumo de oxygeno, le augmento medie del fluxo de sanguine pulmonar esseva 54 pro cento e illo del tension 99 pro cento.

Con le patiente in stato de reposo, per consequente, le constatationes hemodynamic es frequentemente intra le limites del norma; sed exercitio produce alora un augmento anormal del tension, de maniera que le calculate resistentia es augmentate o remane inalterate. Isto es possibilemente le resultato de un augmento del tono vasomotori.

Le constatationes in iste studio se trova in congruentia con le conception que le nivello de tension intra le arteria pulmonar es un del factores que entra in le regulation del grado de tono vasomotori in iste vasos anormal.

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Faraday testified, 'It is quite comfortable to me to find that experiment need not quail before mathematics, but is quite competent to rival it in discovery.' The biologist should not be looked upon with disdain because his studies are sometimes not quantitative in method. Such intellectual snobbishness is not warranted so long as there are highly important fields of investigation to which mathematics, as a mode of expression, is not applicable. It is a satisfaction to know that the eminent physical chemist, G. N. Lewis, has declared, 'I have no patience with attempts to identify science with measurement, which is but one of its tools, or with any definition of the scientist that would exclude a Darwin, a Pasteur, or a Kekule.' To those three may be added Harvey, Virchow, Pavlov, Sherrington and many others.—WALTER B. CANNON, M.D. *The Way of an Investigator.* New York, W. W. Norton & Co., Inc., 1945, p. 35.

Extensive Dermatitis due to Warfarin Sodium (Coumadin)

By CRAWFORD W. ADAMS, M.D., AND BERNARD J. PASS, M.D.

WARFARIN SODIUM, 3-(alpha-acetonylbenzyl)-4-hydroxycoumarin sodium, (Coumadin) is one of several popular anticoagulant agents used to delay intravascular clotting by depression of the prothrombin level of the blood. This drug is often used in instances in which there is an acute thrombophlebitis, pulmonary and peripheral embolism, coronary and cerebral thrombosis, and it is employed prophylactically to prevent arterial embolization and thrombosis.[1-4]

Excessive lowering of circulating prothrombin with spontaneous hemorrhage is the important complication in the use of this prothrombinemic agent.[4, 5] Five per cent of the patients who receive anticoagulant therapy develop mild hemorrhagic manifestations such as hematuria, hemoptysis, epistaxis, and ecchymosis. These are readily controlled by the administration of vitamin K_1. Approximately 2 per cent of patients develop more severe hemorrhagic phenomena such as hemarthrosis, gastrointestinal, cerebral, or subarachnoid hemorrhage, or purpura. These complications demand early recognition and the prompt use of vitamin K_1 or blood transfusion.[6-8]

Sheps and Gifford[9] first reported an allergic manifestation of warfarin sodium. In that instance, transient urticaria appeared in a 50-year-old man, 40 minutes after the oral administration of 50 mg. of warfarin sodium. Subsequently, bishydroxycoumarin was administered without reaction. Extensive dermatitis has not previously been reported as a complication of warfarin sodium therapy.

Case Report

A 63-year-old white man developed an acute inferior myocardial infarction 7 weeks prior to the onset of an acute cerebral arterial thrombosis with aphasia and hemiplegia.

While hospitalized for the myocardial infarction, the patient was treated with bishydroxycoumarin for 17 days. There were no complications, and the patient had an uneventful recovery. Following the extensive cerebral thrombosis, anticoagulant therapy was again initiated. Initially 75 mg. of warfarin sodium were administered, and after 36 hours, the prothrombin level was reduced to 20 per cent of normal. Subsequent prothrombin levels were maintained between 25 and 30 per cent of normal, with a daily dosage of 7.5 mg. of warfarin sodium. After 27 days of anticoagulant therapy, a pruritic, maculopapular, erythematous eruption developed on the face, neck, hands, and forearms. There was no evidence of cutaneous hemorrhage. Examination of the mouth revealed superficial erosions on the buccal mucosa. The eruption on the face and neck resembled the dermatitis seen following unusual exposure to the sun or ultraviolet radiation. There was no previous personal or family history of allergy. The patient was also taking ascorbic acid, nicotinic acid, and phenobarbital, and these were discontinued. Warfarin sodium was continued but the skin manifestations progressed. Three days later, warfarin was discontinued and a combination of pyrrobutamine and thenylpyramine (Copyronil) was administered for 2 days without improvement. Prednisolone, 40 mg., was initiated with a progressive daily reduction in dosage. The oral and the skin lesions immediately improved and disappeared completely 14 days after onset, or 5 days after the initiation of steroid therapy.

After an interval of 10 weeks, 5 mg. of warfarin sodium were again administered daily. After 3 days, the patient again developed pruritus and a recurrence of the oral and superficial cutaneous lesions. Warfarin was discontinued, and the eruption disappeared. A saturated solution of warfarin sodium on sterile gauze was placed upon the patient's forearm for 48 hours. An area, 1.5 x 2.0 cm., of erythema developed without pruritus or induration. Control applications remained clear.

Because of the generalized arterial disease, treatment with bishydroxycoumarin was initiated, and the prothrombin time was maintained between 25 and 30 per cent of normal with 50 mg. daily. After 5 months of therapy there has been no recurrence of allergic manifestations.

The administration of another chemically related anticoagulant, bishydroxycoumarin, without similar allergic manifestations, suggests an absence of cross sensitivity, as noted by Sheps and Gifford.[9]

From the Department of Medicine, Vanderbilt University, School of Medicine, Nashville, Tenn.

Conclusion

Severe dermatitis involving the skin and mucous membranes followed the use of warfarin sodium (Coumadin). Lesions disappeared with steroid therapy but recurred upon challenge with warfarin sodium. Upon elimination of this drug, the skin and oral lesions disappeared. The patient had no allergic manifestations following the administration of bishydroxycoumarin.

Summario in Interlingua

Dermatitis sever, afficiente le pelle e le membranas mucose, sequeva le uso de warfarina a natrium (Coumadina). Le lesiones dispareva con le uso de un therapia steroidic, sed illos recurreva post le provocation con warfarina a natrium. Post le suspension del droga, le lesiones cutanee e oral dispareva. Le patiente habeva nulle manifestationes allergic post le administration de bishydroxycoumarina.

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Of the three characteristics of living tissue—adaptation, growth, and reproduction—the last, reproduction, provides the most searching question to be asked if we want to test for vitality and continuity. Keepers of zoos begin to feel at ease when their more exotic animals succeed in producing their own kind in captivity. Since medical education replenishes the professions that provide medical care, and since medical care is changing in important ways, we must be on guard to make sure that none of the new factors or practices of medical care threatens the continuity of medical education.—ALAN GREGG, M.D. *Challenges to Contemporary Medicine.* New York, Columbia University Press, 1956, p. 87.

Detection of Right-to-Left Shunts with an Arterial Potentiometric Electrode

By LELAND C. CLARK, JR., PH.D., L. M. BARGERON, JR., M.D., CHAMP LYONS, M.D., MERRILL N. BRADLEY, M.D., AND KATRINA T. MCARTHUR, M.D.

THE platinized platinum electrode develops a rapidly responding and readily recorded potential in the presence of hydrogen dissolved in blood. A sensitive procedure for detecting and localizing left-to-right shunts in the catheterization laboratory[1, 2] and in the operating room[3] has been developed with use of such an electrode on the tip of a cardiac catheter.

Hydrogen has been found to be completely cleared from intravenously injected saline solution saturated with hydrogen during its passage through the lungs. Therefore, a test for the detection of right-to-left shunts can be based upon the intravenous injection of saline solution saturated with hydrogen during continuous monitoring for hydrogen in the aorta with a platinum electrode. The localization of such right-to-left shunts, particularly difficult in infants, is determined by a series of injections into the various chambers of the heart. Further, because a platinized platinum electrode develops a potential in the presence of sodium ascorbate,* an injection of this substance serves to verify the responsiveness of the electrode at any time.

It is the purpose of this report to describe the procedure and to illustrate its application in the diagnosis of right-to-left shunts with particular reference to infants.

Methods

Platinum electrodes for use in the artery were prepared by melting a small bead (0.038″) on the end of a 45-cm. length of 28-gage (0.0126″) platinum wire. The wire is then threaded through polyethylene tubing (.023″ I.D. by .038″ O.D.) or polyvinyl tubing (.020″ I.D. by .036″ O.D.) and the bead is sealed in place with a silicone varnish (Dow Corning's 803 resin) or with an epoxy-type cement (for example, Hysol, Houghton Laboratories, Olean, New York). The bead is platinized[2] and the electrode is sterilized by soaking in 70 per cent alcohol or by exposure to ethylene oxide. If vinyl tubing (VX020) Becton, Dickinson, Rutherford, New Jersey) is used, the electrode may be autoclaved.

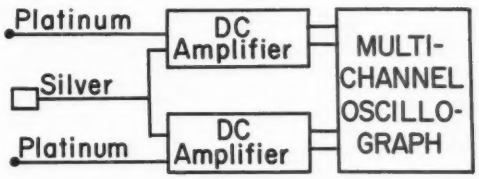

Figure 1

Diagram of circuit for using 2 hydrogen electrodes simultaneously.

In patients, the electrode was threaded into an exposed radial artery, and the tip was advanced under fluoroscopy until it lay in the aorta. In animals, the electrode was fastened to 2 lengths of fine polyethylene tubing in such a way that injections of the hydrogen solution could be made above or below the electrode after it was threaded into the aorta via the femoral artery. This served to tell whether the electrode was pointing up stream or down stream without fluoroscopy.

A silver reference electrode was brought into contact with the cleaned skin with a saline-soaked pad or electrocardiographic paste.

From the Department of Surgery, University of Alabama Medical Center, Birmingham, Ala.

Supported in part by Grant H-3109 from the U. S. Public Health Service and a grant from the Alabama Heart Association.

*The platinum electrode, used as described in this report, namely for the direct recording of potential changes with reference to a common silver electrode, is not to be confused with a similar electrode used for polarographic studies. An extensive study of intravascular polarographic electrodes has been underway in this laboratory for many months and will be published soon. Intravascular polarographic electrodes require the application of polarizing voltages, and the measurement of minute currents; *scrupulous care with insulation* and careful attention to other variables, to be detailed elsewhere, are essential. Potentiometric electrodes, of course, must also be properly insulated but minor breaks in the insulation do not generate "false" currents, as in polarography, but instead cause a loss of signal strength.[4]

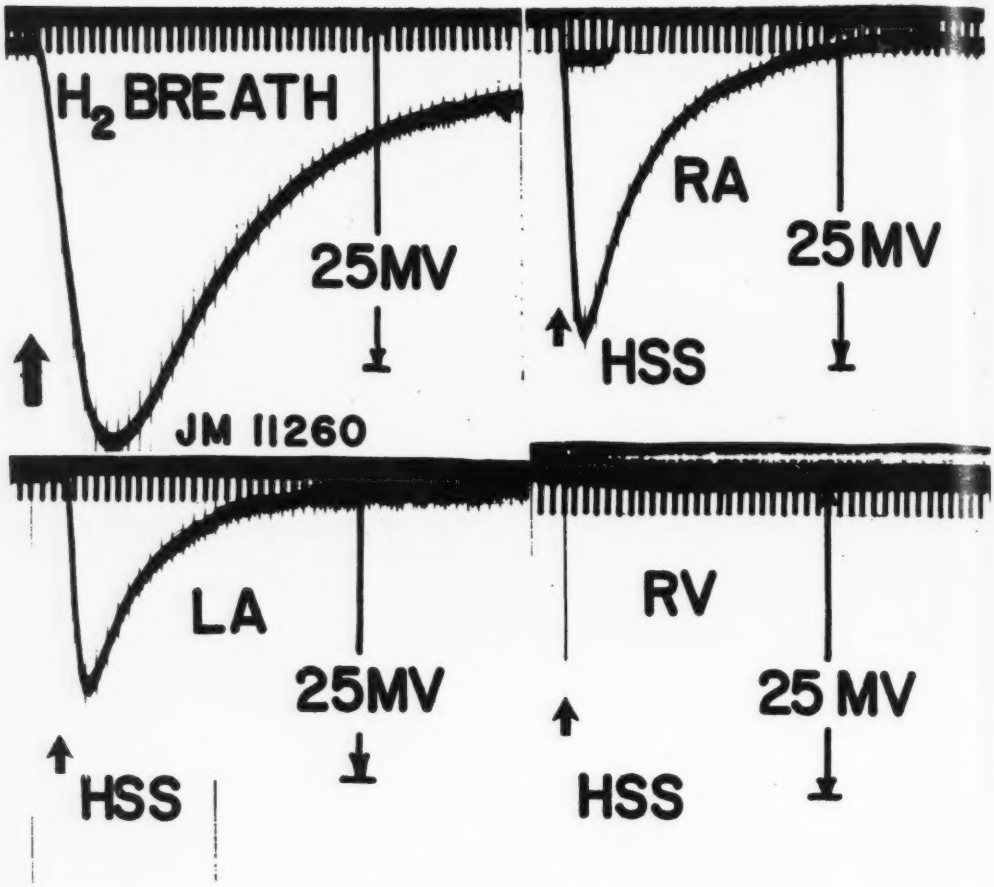

Figure 2

Hydrogen indicator curves in complete anomalous pulmonary venous return and atrial septal defect in 8-month-old infant weighing 5.7 Kg. The curves show responses of the arterial hydrogen electrode to an inhalation of hydrogen (upper left); *to injections of hydrogen saturated saline into the right atrium* (RA), *left atrium* (LA), *and right ventricle* (RV). *The short vertical lines represent 1-second intervals.*

The platinum and silver electrodes were connected directly to the DC input of a recording potentiometer (Varian), a multichannel oscillograph (Electronics for Medicine), or other instruments having a full-scale response of 100 millivolts. When more than one platinum electrode was employed, a single silver electrode was used as a reference for all (fig. 1).

When two electrodes are used simultaneously a common reference electrode may be connected as shown. This simplified hook-up is adequate for most work and may be used instead of the more complex circuit previously published,[2] which included provision for a 50-mv. standardizing signal for each channel. If the reference electrode does not make good contact with the skin, AC interference may appear on the recorder and a brief upswing of the hydrogen curve may occur before it descends following a breath of hydrogen. As many as 4 hydrogen electrodes have been employed simultaneously with use of a single reference electrode.

The 90 per cent response time of the electrode for hydrogen is 0.1 second and for ascorbic acid 0.4 second as measured in a buffer at pH 7.3 at

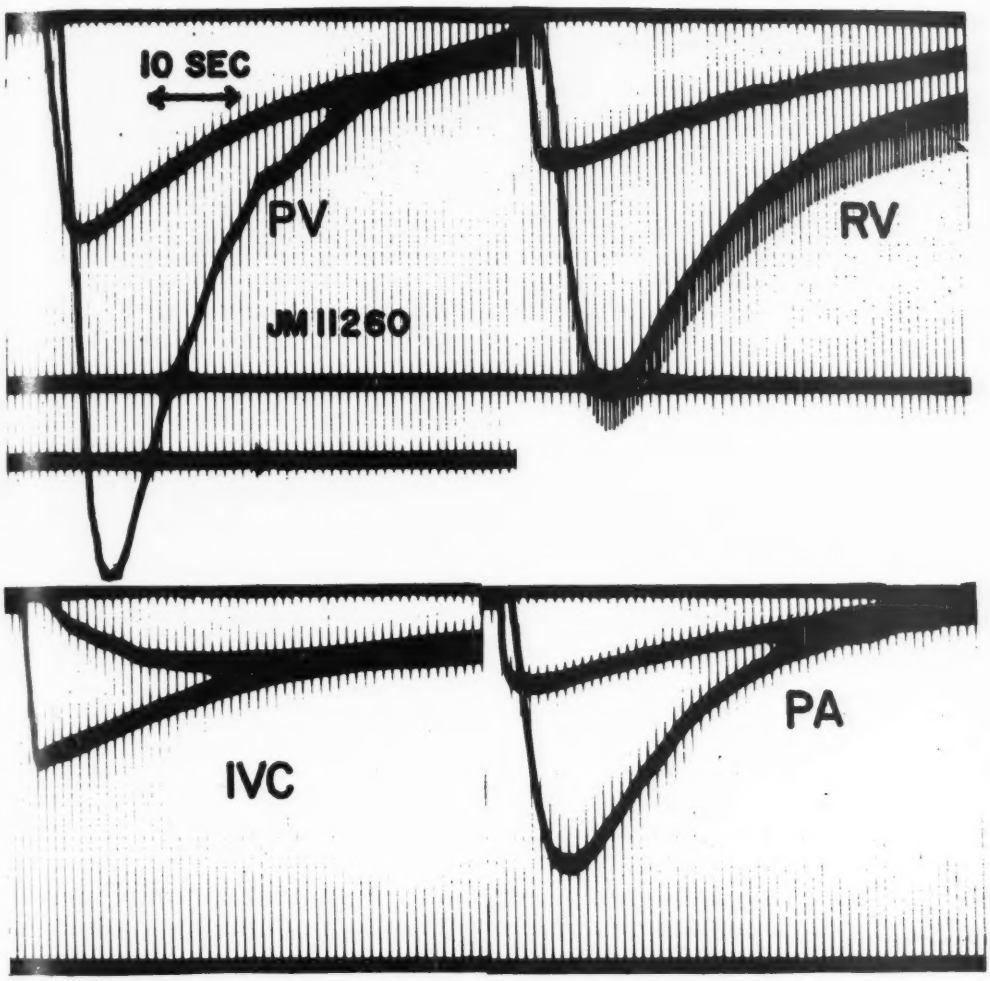

Figure 2a

Hydrogen breathing curves. The patient shown in figure 2 was studied with the venous hydrogen electrode catheter[2] and found to have anomalous venous return. These curves are reproduced here. Tracings obtained with the catheter tip in the anomalous vein, the right ventricle, the inferior vena cava, and the pulmonary artery are shown above. The full-scale setting (black horizontal line at bottom of tracings) was 100 mv. The first downward curve in each of the 4 sets shown above is that of an electrode in the nasal passage which is used as an air-way signal. Note the sharp increase in potential in the tracing obtained from the pulmonary vein and, to a somewhat lesser extent, from all those chambers distal to the shunt.

25 °C. The potential developed in ascorbate solution is approximately doubled if the platinum has been platinized.[1]

After placement of the platinum electrode in the aorta its responsiveness was tested by inhalation of hydrogen and by injection of sodium ascorbate (25 mg.) in saline. If typical sharp responses did not develop, the electrode was moved slightly, since it occasionally was found to be out of the main blood stream and pressing against an arterial wall or to have entered a small arterial branch.

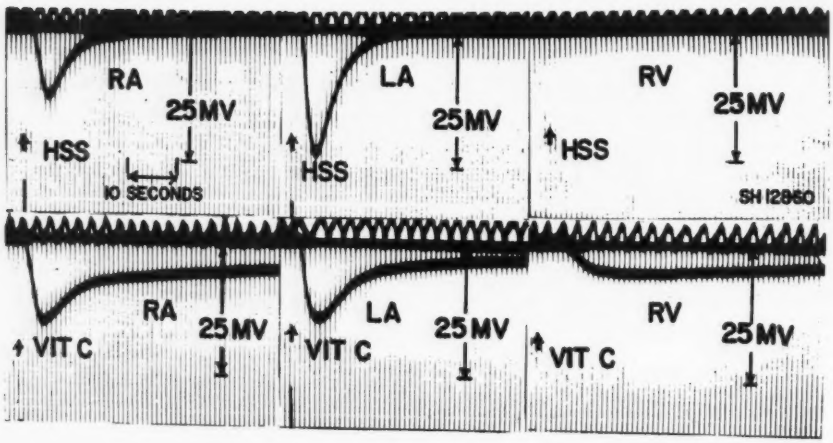

Figure 3

Comparison of hydrogen solution and vitamin C indicator curves in a patient with partial anomalous pulmonary venous return and septal defect. The upper curves were obtained following injection of hydrogen solution into the right atrium, left atrium, and the right ventricle; the lower curves were obtained following injection of ascorbate in these chambers. The injections of ascorbate directly followed those of the hydrogen solution in each case. Note the complete lack of response of the arterial hydrogen electrode following injection of the hydrogen solution into the right ventricle (RV) and the delayed appearance time of the ascorbate. The wavy line along the top of the tracing is from the nasal electrode; it can be seen that the infinitesimal quantity of hydrogen cleared from the hydrogen solution by the lungs is not detected by the nasal electrode. The patient is a 7-year-old girl weighing 42 pounds, who exhibits cyanosis of the nailbeds and lips on exertion. Chest films showed slight cardiac enlargement and increased pulmonary vascularity. The findings on catheterization were consistent with the diagnosis indicated. Sedation: Nembutal and Demerol.

The dose of hydrogen solution and ascorbate most generally suitable was 8 ml. per M.^{2} of body surface although smaller doses may be used. The hydrogen solution was prepared by bubbling hydrogen through normal saline or half saline half glucose solution in a sterile sintered glass Buchner funnel. This procedure saturates the solution with hydrogen and removes the oxygen, further increasing the voltage developed by the platinum electrode. The solubility of hydrogen in aqueous solutions, unlike that of oxygen, does not increase rapidly as the temperature is lowered. Nonetheless, it is preferable to saturate the solution at room temperature, rather than in an ice bath, to avoid the possibility of gas embolism.

Results

Initially a response of approximately 10 mv. was obtained from the aortic electrode in dogs given intravenous hydrogen solution. This response was found to be due to lung damage, induced by a faulty respirator, and to a less extent to a pH effect on the platinum electrode. The electrode responds to a drop in pH as it does to hydrogen. Subsequently hydrogen solution at doses of 0.2, 0.5, and 1.0 ml. per Kg. in dogs showed only an insignificant response (less than 3 mv.); even this could be abolished by adding a few drops of a phosphate buffer (pH 7.4) to the hydrogen solution. In all cases, potential changes greater than 50 mv. were produced by injection of the hydrogen solution directly into the aorta and just above the electrode.

When a lung segment was deliberately damaged by manual compression, positive (right-to-left shunt) arterial responses were observed following injection of hydrogen solution into the vena cava or the right atrium.

The curves in figure 2 illustrate the responses obtained from the arterial electrode

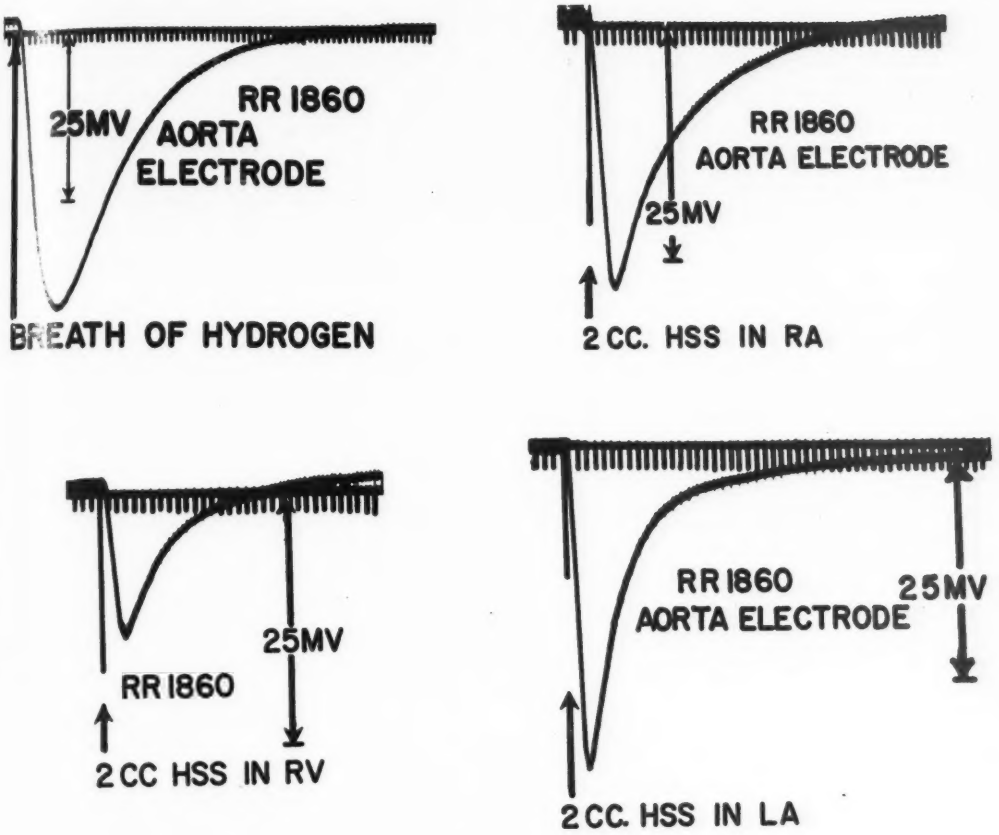

Figure 4

Hydrogen indicator curves in 4-month-old boy with tetralogy of Fallot. The upper left *curve, after a breath of hydrogen, served to verify the reactivity of the arterial electrode. Injections of hydrogen solution into the left atrium (LA), through a patent foramen ovale (*lower right *curve) also verified the reactivity of the electrode and is shown for comparison. The positive responses obtained following injections into the right atrium (*RA*) and the right ventricle (*RV*) indicate the shunt is in, or distal to, the ventricle. Verticle lines are 1-second intervals.*

in an infant having a right-to-left shunt. Positive arterial curves were obtained following a breath of hydrogen, and injections (via a patent foramen ovale) into the left atrium indicating that the electrode was properly placed. Positive responses were obtained also following injection into the right atrium but not into the right ventricle, indicating a shunt at the atrial level. (Figure 2*a* shows the curves obtained at routine hydrogen electrode catheterization.)

The potential curves recorded from the arterial electrode following the injection of hydrogen solution and vitamin C into the right and left atrial and into the right ventricle are compared in figure 3. Repeated injections of hydrogen solution into the right ventricle failed to indicate the presence of hydrogen in the aorta, whereas vitamin C always appeared. Positive responses for both vitamin C and hydrogen solution were obtained after injections into the left atrium

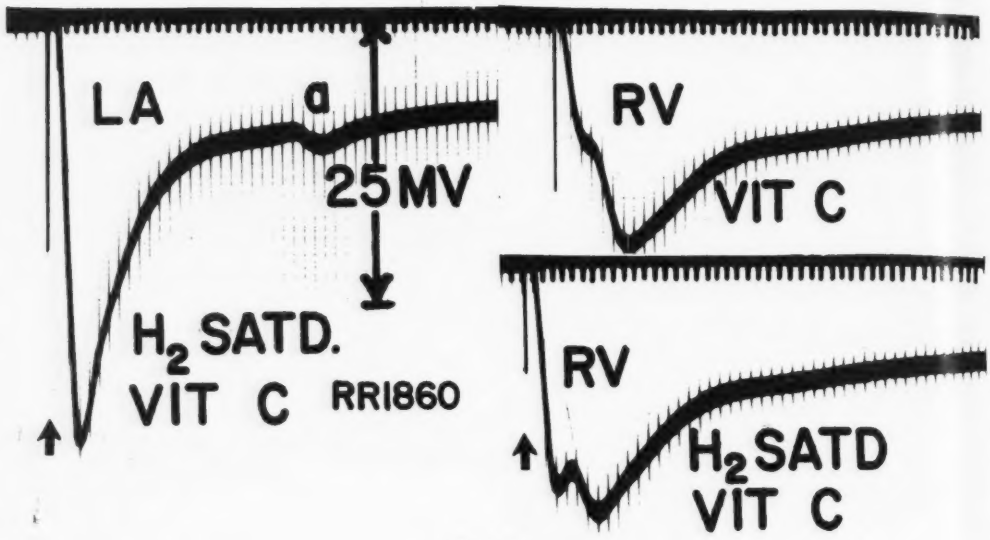

Figure 4a

Hydrogen saturated sodium ascorbate solution as an indicator. To obtain the upper right curve, 2 ml. (50 mg.) of sodium ascorbate in saline were injected into the right ventricle. In the lower right, the ascorbate was saturated with hydrogen before injection. Note the increase in the initial hump on the curve. This increase corresponds with the hydrogen peak (fig. 4) in which the same patient is presented. On the left, the curve obtained by injecting hydrogen saturated ascorbic acid into the left atrium is shown for comparison; the portion indicated by "a" is an artifact. Vertical marks are 1-second intervals.

and right atrium. Together these tests demonstrate the presence of a right-to-left shunt through an atrial septal defect. A double-humped vitamin C curve was not observed, probably because the shunt was small and circulation time short.

In figure 4 are shown the curves obtained following hydrogen breathing and hydrogen solution injection in an infant with tetralogy of Fallot. In this patient a "control" injection distal to the shunt could not be made because the catheter could not be passed safely through the severe infundibular stenosis. The responses to the injections indicate a shunt at or beyond the ventricular level. To illustrate further the application of the present technic a series of injections of sodium ascorbate and hydrogen saturated solutions was employed. Figure 4*a* shows that the initial hump on the ascorbate curve, clearly evident in this patient, is increased by adding hydrogen to the ascorbate solution.

Discussion

The complete clearing of hydrogen from intravenously injected solutions makes possible a delicate test for right-to-left shunts. The rapid and sensitive response of the electrode makes it possible to obtain diagnostic curves in infants. The response of the electrode to ascorbate is slower than to hydrogen but is still rapid enough to be used to confirm the reactivity of a given electrode in a particular patient. It is hoped that a redox-active solution can be found that will produce even sharper responses.

Since the diagnosis rests essentially on both positive and negative responses, a series of injections into various chambers is required. That a negative response is not due to a failure of the detecting electrode can be assured by testing the electrode by hydrogen breathing, by injecting sodium ascorbate solution, by injecting hydrogen solution into the left atrium, and by injecting hydrogen solution

proximal to the suspected shunt. That a positive response is not due to a defect in the lungs can be ruled out in a given patient by a negative response proximal to the shunt. It appears from the experimental work as well as from the clinical tests that "false positive" arterial responses do not occur in the absence of lung disease.

The sensitivity of the test can be realized from the observation that as little as 0.1 ml. of hydrogen solution injected directly into the aorta is easily detected by the arterial electrode. This amount of hydrogen solution contains only 0.002 ml. of dissolved hydrogen.

The procedure is relatively simple and inexpensive. The hydrogen is nontoxic and rapidly cleared from the circulation, thus permitting as many injections as consideration of fluid volume allows. Sodium ascorbate solutions appear to be completely innocuous. There is the hazard of working with hydrogen. Reasonable caution must be used particularly in the storage of large (and possibly leaky) hydrogen tanks.

By placement of the indicator detector (the platinum bead) in the aortic arch concentration changes are more rapidly and faithfully recorded than in a system in which samples are withdrawn through a long narrow arterial catheter.

Summary

Saline solution saturated with hydrogen is completely cleared of hydrogen in passing through the normal lung. The presence of dissolved hydrogen, which can be detected with a platinum electrode, in the aorta following the injection of hydrogen saturated solutions into the right heart is therefore diagnostic of a right-to-left shunt. Localization of the shunt is made by a series of injections into the various chambers of the heart. Since the electrode also responds to increased concentrations of sodium ascorbate, this substance can be used as an indicator in itself and as a test to establish the functional ability of the aortic electrode. The sensitivity and speed of the response of the electrode, together with the relative simplicity and inexpensiveness of the procedure, makes the technic readily adaptable to routine diagnostic catheterizations in infants.

Acknowledgment

The authors wish to thank the Upjohn Company for the ascorbic acid (1000 mg. per 10 ml., sodium bisulfite 10 mg., buffered with sodium bicarbonate) used in this work. Special thanks are given to Paul Boyles and Joe Gilmer for technical assistance. Clarence Forrest and Phillip Kelly assisted in the experimental work.

Summario in Interlingua

Un solution salin que es saturate con hydrogeno perde su hydrogeno completemente in su passage a transverso le pulmon normal. Per consequente, le presentia de hydrogeno dissolute, detegibile per medio de un electrodo de platino, in le aorta subsequente al injection de solutiones a saturation hydrogenic in le corde dextere suffice a establir le diagnose de derivation dextero-sinistre. Le localisation del derivation pote esser effectuate per medio de un serie de injectiones in 1 varie cameras del corde. Viste que le electrodo responde etiam a augmentate concentrationes de ascorbato de natrium, iste substantia pote esser utilisate como indicator per se e como un test pro establir le capacitate functional del electrodo aortic. Le sensibilitate e le rapiditate del responsa del electrodo, insimul con le simplicitate relative e le basse costo del technica, recommenda lo al uso in catheterismo diagnostic routinari in infantes.

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The Vectorcardiogram in the Differential Diagnosis of Atrial Septal Defect in Children

By JEROME LIEBMAN, M.D., AND ALEXANDER S. NADAS, M.D.

THE COMMONEST types of atrial septal defects are the high ostium secundum defects frequently associated with pulmonary venous anomalies, and the low ostium primum lesions almost invariably accompanied by atrioventricular valve clefts, less often by a high ventricular septal defect. To encompass the entire spectrum of variations involving defects low in the atrial septum, high in the ventricular septum, and one or both atrioventricular valves, we have adopted the embryologic term "endocardial cushion defect" following the suggestion of Watkins and Gross.[1]

There are 2 principal reasons for trying to differentiate endocardial cushion defects from those of the ostium secundum: the prognosis is usually worse in the former, thus surgery is more urgent; open-heart surgery only by means of a pump oxygenator is capable of solving the complex deformities of the endocardial cushion defects, whereas closed surgical technics and hypothermia are being successfully applied in the correction of ostium secundum lesions.

The electrocardiogram has been more help-

From the Sharon Cardiovascular Unit of the Children's Medical Center and the Department of Pediatrics of the Harvard Medical School, Boston, Massachusetts.

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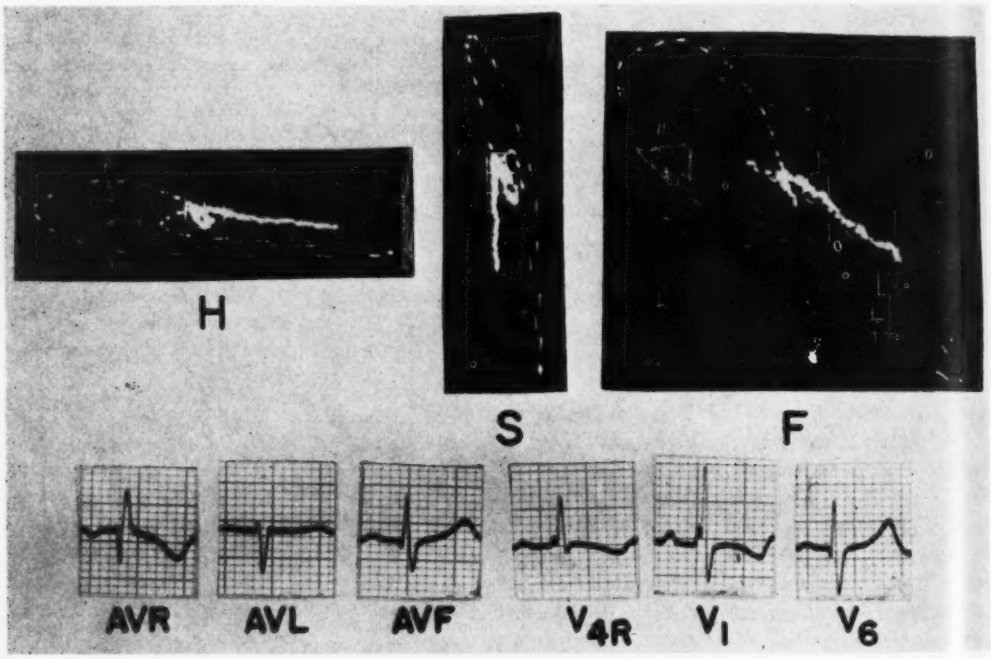

Figure 1

Typical atrial septal defect of the secundum type in patient R.M., age 9. The horizontal plane is inscribed clockwise, the sagittal plane counterclockwise, indicating right ventricular hypertrophy. The frontal plane is clockwise. Note the prominent terminal rightward appendage.

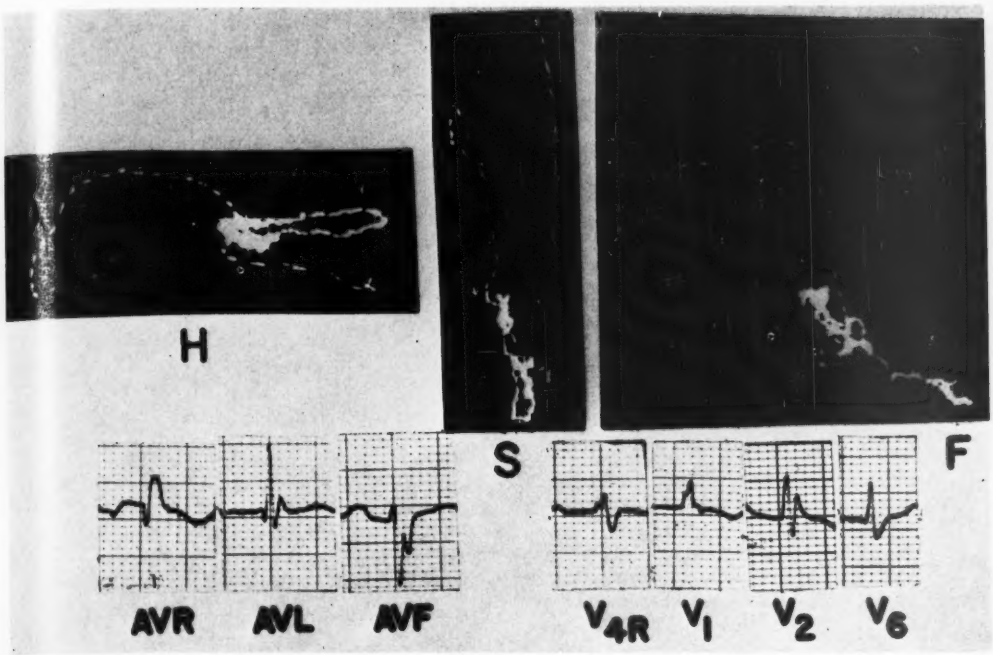

Figure 2

Typical endocardial cushion defect in patient P.T., age 9½. Most of the horizontal plane is inscribed clockwise and the sagittal plane is counterclockwise, indicating right ventricular hypertrophy. Note, however, that the frontal plane is counterclockwise and the sagittal and frontal planes are superiorly oriented. Also, the terminal rightward appendage is even more prominent than in figure 1.

ful than any other tool in the differential diagnosis of the 2 conditions, right axis deviation being present in ostium secundum defects, left axis deviations in the others. However, the occasional QRS frontal plane axis around 0° and axes perpendicular to the frontal plane have tended to create difficulties. It was hoped that the vectorcardiogram might furnish more specific information in this regard and at the same time shed some light on the nature of the rsr′ pattern so commonly observed in patients with atrial septal defects, as well as in some normal children. Furthermore, we were interested in correlating the vectorcardiographic patterns in these patients with the available hemodynamic data.

Material and Methods

The study was preceded by a quantitative analysis of the Grishman cube vector in 135 normal children, aged 2 through 14.[2] Normal standards for comparison were thus established and have been included in the tables of data.

There was a total of 32 atrial septal defects of the secundum type. The diagnosis was made by operation in 17, by typical cardiac catheteri-

Table 1

Duration of QRS

	Category	Mean	Range
135	Normal	.061	(.050-.078)
17	Proved ostium secundum defects	.085	(.065-.107)
32	Total ostium secundum defects	.084	(.063-.107)
16	Proved endocardial cushion defects	.084	(.062-.107)
32	Total endocardial cushion defects	.087	(.058-.115)
4	Ostium secundum defects with atrioventricular clefts	.080	(.070-.092)
2	Ventricular septal defects with tricuspid valve clefts		.088 and .093

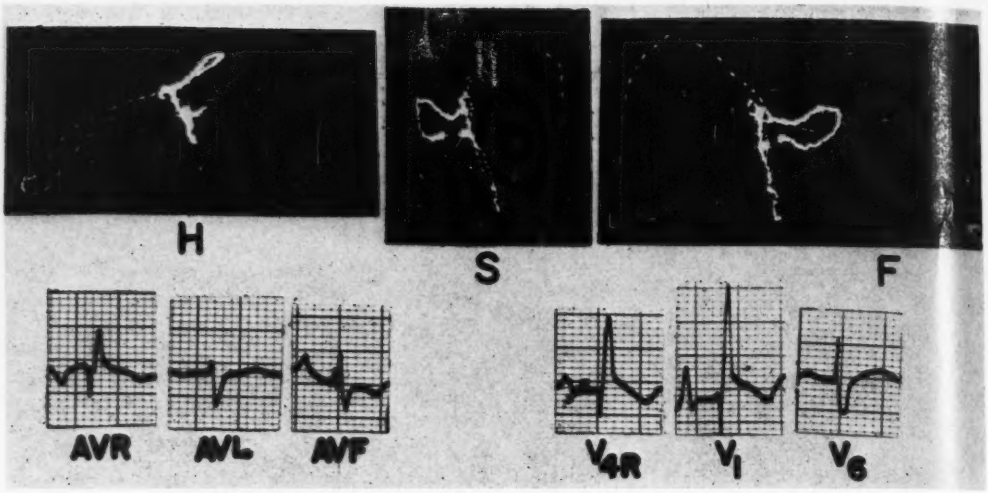

Figure 3

Atypical ostium secundum defect with right bundle-branch block and right ventricular hypertrophy in patient K.C., age 9. Note the classical rightward, anterior terminal appendage with terminal slowing in all 3 planes. The inscriptions in the horizontal and frontal planes are counterclockwise.

Table 2

Linear Measurements in Millivolts

Right	Left	Individual Left/Right	Anterior	Posterior	Individual Pt/At	Inferior	Superior	Individual Superior/Inferior
			135 Normals					
.08 (0-0.31)	0.60 (0.21-1.17)	6.67 (∞-1.89)	0.15 (0.01-0.36)	0.11 (0-0.40)	0.9 (0-6.6)	0.85 (0.14-1.33)	0.10 (0-0.38)	0.20 (0-0.80)
			17 Proved ostium secundum defects					
0.40 (0.20-0.66)	0.67 (0.36-1.90)	1.9 (0.6-6.7)	0.26 (0.10-0.48)	0.04 (0-0.10)	0.2 (0-1.0)	0.60 (0.24-0.90)	0.20 (0.08-0.48)	0.4 (0.1-0.8)
			32 Total ostium secundum defects					
0.44 (0.20-1.14)	0.66 (0.36-1.90)	1.8 (0.3-6.7)	0.28 (0.02-0.62)	0.04 (0-0.14)	0.3 (0-1.6)	0.60 (0.24-2.10)	0.22 (0.04-0.66)	0.4 (0.1-0.8)
			16 Proved endocardial cushion defects					
0.50 (0.22-1.34)	0.44 (0.10-0.96)	1.2 (0.2-6.4)	0.26 (0.04-0.80)	0.02 (0-0.12)	0.3 (0-1.5)	0.42 (0.10-0.62)	1.20 (0.20-1.24)	2.3 (0.7-3.5)
			23 Total endocardial cushion defects					
0.50 (0.10-1.34)	0.48 (0.10-1.52)	1.6 (0.1-6.4)	0.24 (0.04-0.80)	0.04 (0-0.16)	0.5 (0-2.5)	0.40 (0.10-1.04)	0.90 (0.20-1.34)	2.5 (0.7-9.0)
			4 Ostium secundum defects with atrioventricular cleft					
0.58 (0.30-0.96)	1.08 (0.28-1.62)	2.3 (0.5-4.8)	0.28 (0.16-0.52)	0.06 (0-0.20)	0.1 (0-0.3)	0.62 (0.38-0.76)	0.42 (0.20-0.66)	0.7 (0.4-0.9)
			2 Ventricular septal defects with tricuspid valve clefts					
0.12 0.38	1.20 1.32	10.0 3.5	0.10 0.28	0.10 0	1.0 0	0.34 0.86	0.52 0.32	1.6 0.4

Figures listed are averages with the range of variation in parentheses.

Right and left forces from horizontal and frontal planes. Anterior and posterior forces from horizontal and sagittal planes. Inferior and superior forces from sagittal and frontal planes. The individual ratios (left:right, posterior:anterior, superior:inferior.) are obtained by calculating the ratio in each vectorcardiogram, then making an average of all.

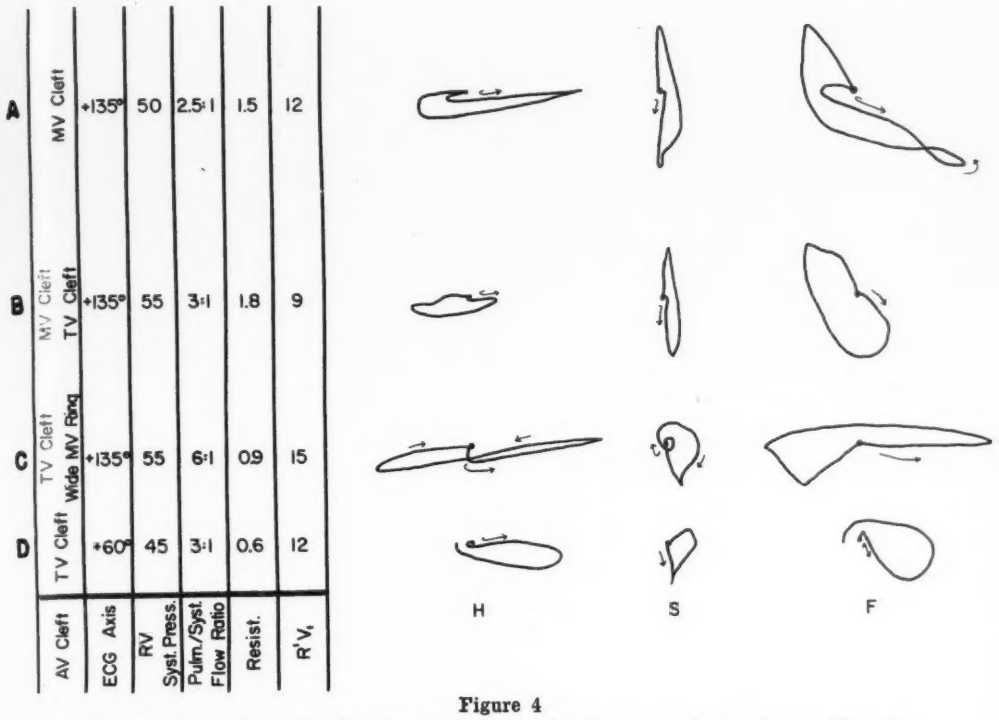

Figure 4

Drawings to scale of the 4 vectorcardiograms of ostium secundum defects with atrioventricular valve clefts, together with pertinent electrocardiographic and hemodynamic data. Even when mitral valve clefts are present, a superior orientation is not seen.

zation and clinical data in 7, and by classical clinical data alone in 8.

There were 23 patients with endocardial cushion defects. The diagnosis was proved by operation or autopsy in 16, and by classical clinical and catheterization data in 7.

Six additional patients did not fit clearly into either group, but are included because they were thought to have left-to-right shunts at the atrial level on the basis of cardiac catheterization. Two of these proved at operation to have a ventricular septal defect with tricuspid regurgitation due to a cleft in the valve. The other 4, though clinically resembling endocardial cushion defects, had ostium secundum defects with mitral or tricuspid valve clefts.

The vectorcardiograms were obtained according to a modification of the Grishman cube technic[3] with a Sanborn vector amplifier, and were photographed with a 35-mm. Dumont Oscillograph-Record Camera. The vector loop was interrupted every .0025 second for accurate timing. Each resultant line was in the form of a teardrop, so that the direction of inscription could easily be seen. The QRS loops were magnified on a Model R Documat roll film reader, and were transcribed exactly to scale on graph paper. These drawings could then be examined repeatedly for measurement and comparison. The mean axis could also be estimated by bisecting the area of each vector loop.

Cardiac catheterizations were all performed in the cardiopulmonary laboratory of the Children's Medical Center by methods previously described.[4] Right ventricular systolic pressures, pulmonary/systemic flow ratios, and right ventricular/left ventricular work ratios, were correlated with the vectorcardiograms. Work was calculated by the following formulas:[5] 1. RV work = pulmonary flow X (PA mean pressure − RA mean pressure) X 1.36 X 10^{-2} Kg. M./min. 2. LV work = systemic flow X (BA mean pressure = Pc mean pressure) X 1.36 X 10^{-2} Kg. M./min. Whenever the systolic gradient across the pulmonic valve exceeded 25 mm. mercury, right ventricular mean systolic ejection pressure was substituted for pulmonary artery mean pressure.

Table 3

Mean QRS Axis in the Frontal Plane

Average and range	+90° or>	+60→+89	+30→+59	0→+29	0→—29	—30→—59	—60→—89	—90 or<
135 Normal: +59° (+20°→+80°)	0	78	53	4	0	0	0	0
17 Proved ostium secundum defects* +101° (+30°→+170°)	10	5	2	0	0	0	0	0
32 Total ostium secundum defects* +96° (+30°→+170°)	18	9	5	0	0	0	0	0
16 Proved Endocardial cushion defects −81° (+35°→−175°)	0	0	1	0	1	3	3	8
23 Total endocardial cushion defects −78° (+35°→−175°)	0	0	1	1	2	3	6	10
4 Ostium secundum defects with atrioventricular clefts +10°, +130°, +135°, +170°	3	0	0	1	0	0	0	0
2 Ventricular septal defects with tricuspid valve defects −10° + +100°	1	0	0	0	1	0	0	0

*One patient with ECG axis perpendicular to frontal plane had VCG frontal plane axis of +120°.

Results

QRS Duration

Measurement of QRS duration by vectorcardiogram is considerably more accurate than that obtained by conventional scalar leads, since the inscription is interrupted every .0025 second. At the most the error in analysis will be 1 or 2 dots, and thus .0025 or .0050 second. There was no significant difference in the QRS durations among any of the groups (table 1).

Linear Measurements

As can readily be seen in table 2, the vector loops of normal patients are predominantly to the left, whereas those of both groups of atrial septal defects are approximately as far to the right as to the left, indicating right ventricular hypertrophy. The individual left : right ratios also point in the same direction. The anterior and posterior forces seem to be of equal magnitude in the normal group, whereas the anterior ones dominate in both major groups. This finding adds confirmatory evidence for right ventricular hypertrophy without distinguishing between ostium secundum and endocardial cushion defects. All but 1 patient had right ventricular hypertrophy by these definitions.[6, 7] The inferior forces dominate in normal subjects as well as in those with ostium secundum lesions, whereas in the group of endocardial cushion defects, the superior forces are larger.

Thus the relationships of rightward to leftward and anterior to posterior forces help to distinguish atrial septal defects from normal tracings, whereas analysis of the superior and inferior forces distinguish the 2 major varieties from each other.

The linear measurements of the 4 cases with atrial septal defects of the ostium secundum type with atrioventricular valve clefts were very similar to ostium secundum lesions in general, except for a somewhat more leftward tendency, and, in contrast to the clinical profile, were sharply different from the endocardial cushion defects. No conclusions can

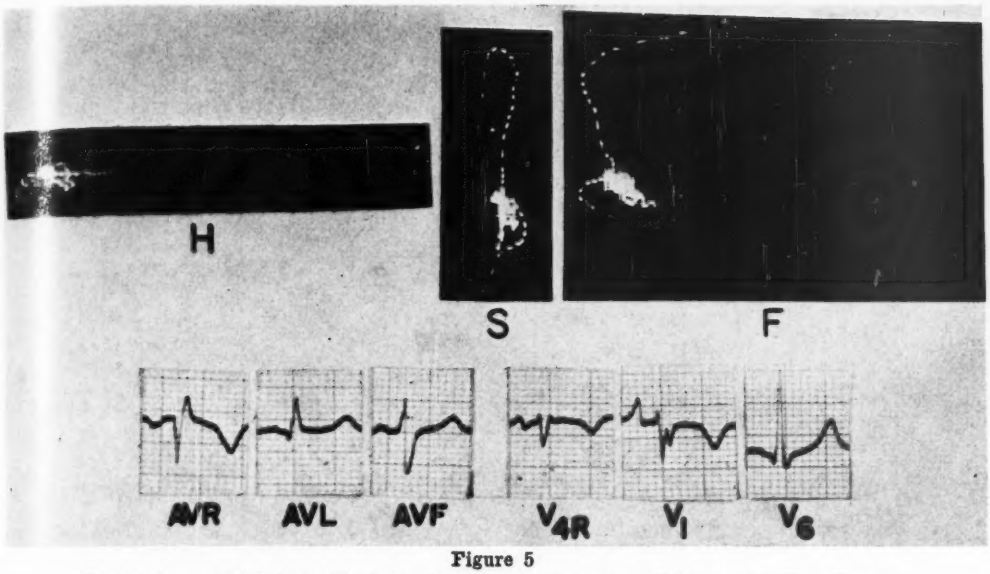

Figure 5

Ventricular septal defect with cleft tricuspid valve in patient M.C., age 14. Hemodynamic data indicated a left-to-right shunt at the atrial level. There is no evidence for right ventricular hypertrophy, since the loops extend only briefly to the right and anteriorly with a normal direction of inscription in each plane.

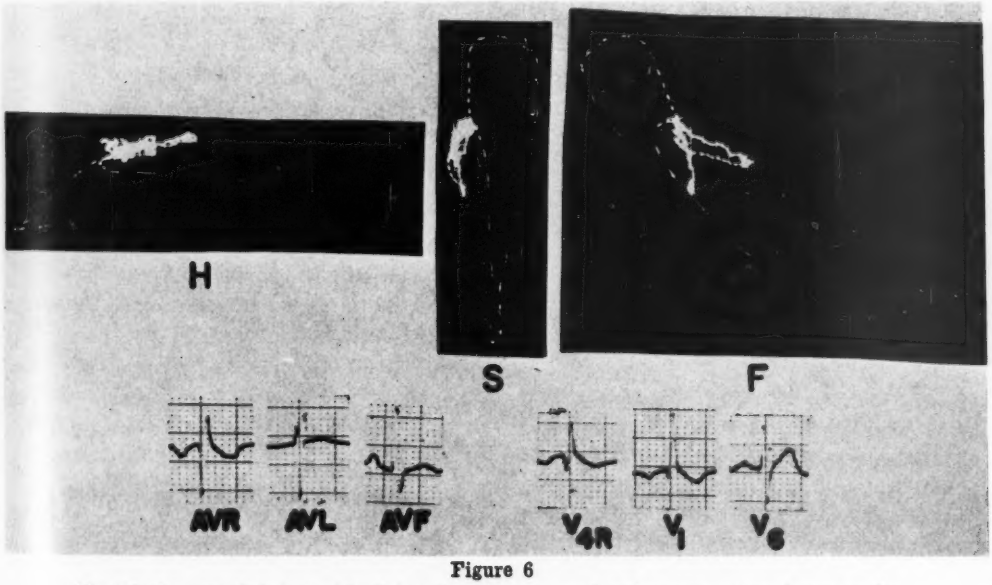

Figure 6

Ventricular septal defect with cleft tricuspid valve and pulmonary artery hypertension, and a left-to-right shunt at the atrial level in patient J.E., age 2½. The counterclockwise frontal plane loop in the presence of considerable right ventricular hypertrophy probably indicates additional left ventricular hypertrophy and is much against the diagnosis of an ostium secundum lesion. The inferior orientation is against the diagnosis of an endocardial cushion defect.

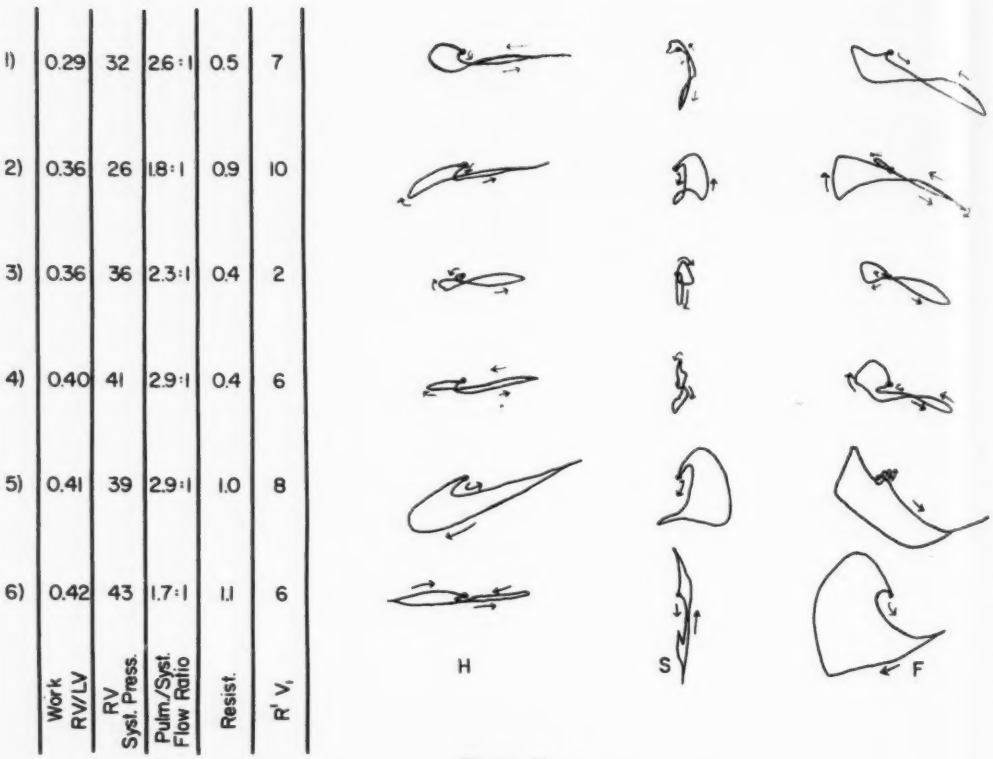

Figure 7

Scale drawings of the vectorcardiograms of catheterized patients (nos. 1-6) with ostium secundum defects listed in order of increasing right ventricular/left ventricular work ratios. Hemodynamic data and the height of R' in V_1 of the electrocardiogram are also included.

be drawn from the 2 cases of ventricular septal defect with tricuspid valve clefts.

Mean QRS Axis in the Frontal Plane

The normal mean electrical axis as determined from the frontal QRS vector loop ranges from +20° to +80°, representing a much narrower normal range than obtained by conventional scalar electrocardiography (table 3). The ostium secundum defects average considerably to the right of normal, whereas the endocardial cushion defects are far to the left, there being minimal overlapping in the +30° to +59° range.

Of the 4 atypical cases of atrial septal defect of the secundum type, 3 had mean electrical axes over +90°. No significant conclusion may be drawn from the 2 patients with ventricular septal defect and tricuspid valve cleft.

It should be emphasized that the mean electrical axis in the frontal plane is but one expression of the balance of all the linear forces, although the influence of the superior and inferior forces seems to be most important.

The advantage of obtaining the mean electrical axis by vector methods rather than by conventional leads is well demonstrated in one of the patients. This child with a proved atrial septal defect of the secundum type had no determinable axis in the frontal plane of the electrocardiogram, whereas in the vectorcardi-

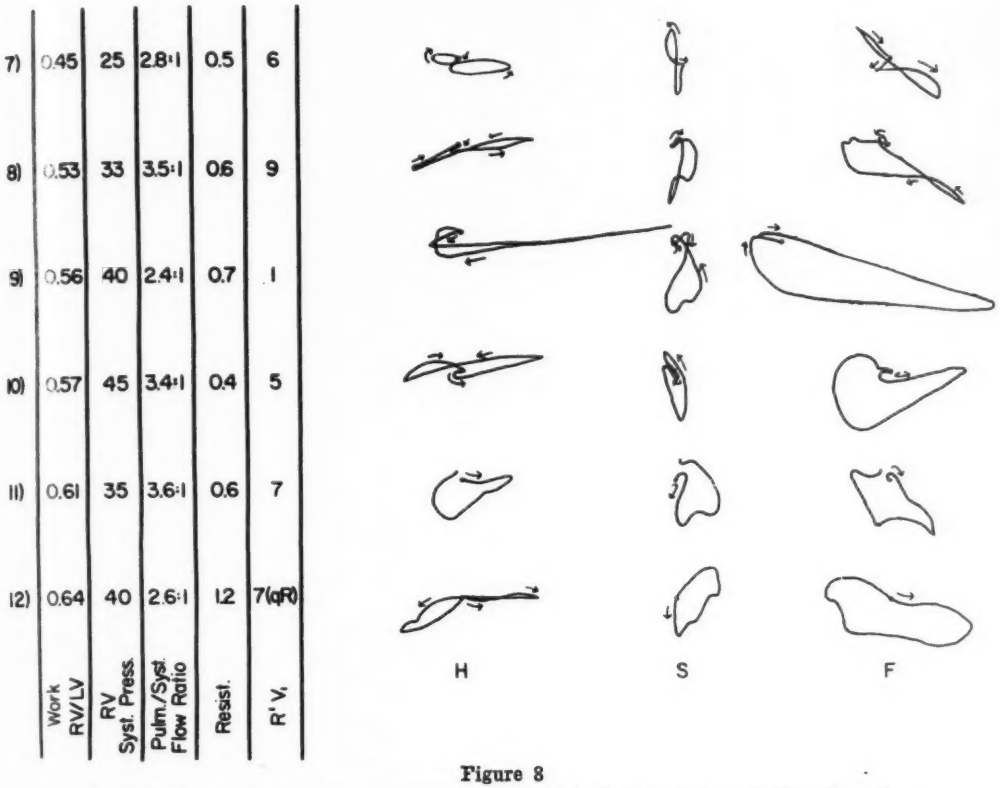

Figure 8

Scale drawings of the vectorcardiograms of catheterized patients (nos. 7-12) with ostium secundum defects. (See legend for figure 7.)

ogram the axis fell into the range characteristic of the defect (+120°).*

Vector Patterns in the Two Major Groups

Horizontal Plane

The majority of patients in both major groups had similar patterns in the horizontal plane. Initially the loop goes briefly to the right and anterior. Then it turns sharply to the left for some distance, only to turn right again, clockwise, inscribing a more or less narrow loop. Finally it terminates in a large clockwise loop to the right of the 0 point either anteriorly or posteriorly (figs. 1 and 2).

There were variations of this typical pattern. Three of the ostium secundums and 7 of the endocardial cushion defects had no initial rightward force. Instead of the typical clockwise inscribed body, 13 of the ostium secundums and 10 of the endocardial cushion defects were counterclockwise or crossed over. The terminal forces were not clockwise in 2 of the ostium secundum lesions and 7 of the endocardial cushion defects.

Thus the horizontal plane is not particularly useful in differentiating between ostium secundum and endocardial cushion defects, though with numerous variations it presents

*Since the preparation of this article 2 other children with nondeterminable axes in the frontal plane of the electrocardiogram were correctly diagnosed with the help of the vectorcardiogram. One patient had a positive axis and an atrial septal defect of the secundum type. The other patient's vectorcardiogram demonstrated a negative axis in the frontal plane. At surgery an endocardial cushion defect was demonstrated.

	Work RV/LV	RV Syst. Press.	Pulm./Syst Flow Ratio	Resist.	R' V_1
13)	0.65	39	2.3:1	0.4	11
14)	0.78	42	1.8:1	1.4	13
15)	0.92	60	2.1:1	1.0	7
16)	0.94	40	3.4:1	0.7	7
17)	0.97	48	4.0:1	0.4	11
18)	1.36	42	42:1	0.9	8

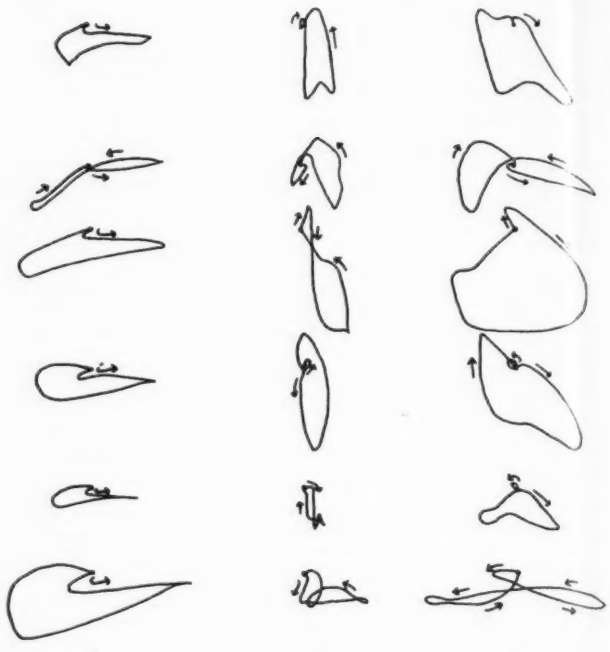

Figure 9

Scale drawings of the vectorcardiograms of catheterized patients (nos. 13-18) with ostium secundum defects. (See legend for figure 7.)

a pattern characteristic of right ventricular hypertrophy.[3, 6]

Sagittal Plane

The body of the vector loop in the sagittal plane is superiorly directed in endocardial cushion defects and inferiorly in ostium secundum lesions (figs. 1 and 2). There was only 1 exception to this rule among our 55 patients in the 2 major groups. One vectorcardiogram, which otherwise was quite characteristic of an endocardial cushion defect, exhibited equal superior and inferior forces in the sagittal plane.

The initial forces in the majority of the ostium secundum lesions are directed upwards. The body is inscribed counterclockwise, anteriorly, and is directed inferiorly. The terminal forces are superior, occasionally inferior, and may be anterior or posterior.

The initial forces in the majority of the endocardial cushion defects are inferiorly directed. Then the loop turns superior and anterior with the inscription of the body in either direction. The terminal forces are located inferiorly or superiorly, and anterior or posterior.

There are exceptions to these typical patterns. Some of the initial forces in either group may be directed in the opposite direction. Although the body of the ostium secundum loop was usually counterclockwise, a few were crossed over or inscribed clockwise.

Right ventricular hypertrophy is demonstrated in this plane by the occurrence of an

Table 4

Ostium Secundum Defects (Vector Analysis versus Work Ratio)

Patient no.	Right	Anterior	Right/Left	Superior/ Inferior	Right + anterior— left + posterior*	Right + anterior/ left + posterior†	Frontal plane angle
1	0.34	0.16	0.4	0.1	−0.54	0.5	+75°
2	0.52	0.26	0.7	0.5	−0.02	1.0	+170°
3	0.26	0.14	0.5	0.5	−0.14	0.7	+40°
4	0.34	0.08	0.5	0.6	−0.28	0.6	+120°
5	0.48	0.48	0.5	0.5	−0.18	0.8	+110°
6	0.66	0.10	1.2	0.5	+0.14	1.2	+150°
7	0.28	0.12	0.6	0.8	−0.14	0.7	+95°
8	0.40	0.22	0.6	0.1	−0.12	0.8	+110°
9	0.28	0.02	0.2	0.2	−1.62	0.2	+35°
10	0.48	0.10	0.7	0.3	−0.32	0.7	+105°
11	0.28	0.38	0.7	0.3	+0.24	1.6	+105°
12	0.60	0.34	0.9	0.6	+0.28	1.4	+100°
13	0.30	0.34	0.5	0.3	+0.06	1.1	+90°
14	0.50	0.38	0.7	0.6	+0.04	1.1	+120°
15	0.62	0.42	1.2	0.2	+0.32	1.4	+80°
16	0.48	0.24	0.8	0.4	+0.08	1.1	+80°
17	0.34	0.20	0.9	0.2	+0.16	1.4	+70°
18	0.80	0.58	0.9	0.8	+0.46	1.5	+95°
19	0.22	0.16	0.3	0.1	−0.30	0.6	+75°
20	0.60	0.66	1.0	0.3	+0.60	1.9	+125°
21	1.14	0.62	3.0	0.5	+1.38	4.6	+105°
22	0.62	0.60	1.7	0.8	+0.76	2.7	+155°

Patients listed in order of increasing severity of right ventricular/left ventricular work. Linear measurements are in millivolts. The exact work ratios can be found in figures 11-14.

*Calculated by adding the right plus anterior linear measurements and subtracting the sum of the left plus posterior measurements.

†Calculated by adding the right plus anterior linear measurements and dividing this sum by the sum of the left plus posterior measurements.

anterior loop in both defects. Further evidence of right ventricular predominance is found if the loops are inscribed counterclockwise or are crossed over, as is the case in 29 of the 32 ostium secundum lesions and 14 of the 23 endocardial cushion defects. If the anterior loop is inscribed clockwise, it may mean less right ventricular hypertrophy, as in the 3 atrial septal defects of the secundum type, or additional left ventricular hypertrophy, as in the 9 endocardial cushion defects.

Frontal Plane

The QRS loops in the ostium secundum lesions in the frontal plane—as in the sagittal plane—are inferior. In addition, most of them are inscribed clockwise. The initial forces are mostly to the right, but superior or inferior, and clockwise.

The QRS loop in the endocardial cushion lesions is superior and mostly counterclockwise. The initial forces are to the right and inferior while the terminal forces are to the right and superior or inferior, and counterclockwise.

Again there are exceptions to these typical patterns in all segments of the loop. Seven patients with ostium secundum lesions did not have wholly clockwise loops. Four of these were calculated to have the smallest right ventricular work loads, 2 had patterns of right bundle-branch block (fig. 3), and a seventh also had a conduction disturbance. (In only 3 of the 55 patients in this series was right bundle-branch block diagnosed by Grishman's criteria.[8]) Five patients among the group with endocardial cushion defect did not have wholly counterclockwise loops. Four of these were calculated to have very high right ventricular work loads.

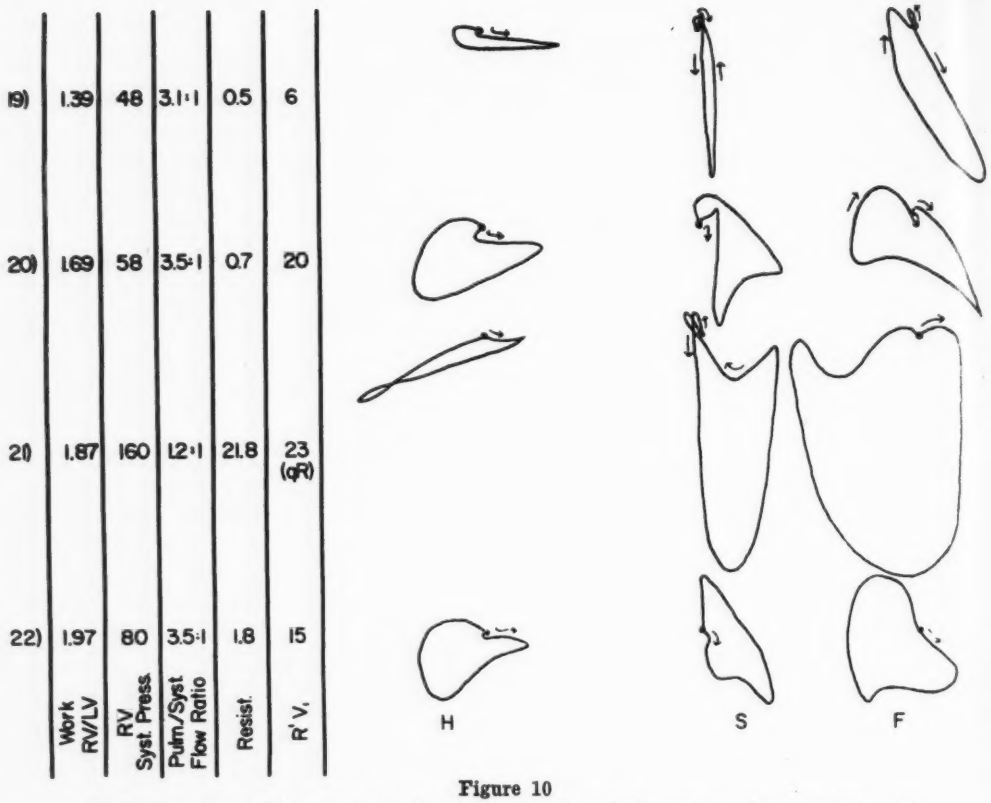

Figure 10

Scale drawings of the vectorcardiograms of catheterized patients (nos. 19-22) with ostium secundum defects. (See legend for figure 7.)

In the frontal plane, then, the 2 major types of atrial septal defects showed opposite superior and inferior forces as well as different directions of inscription. In addition, clockwise inscription in both defects seemed to indicate high right ventricular work loads.

Vector Patterns in the Two Unusual Groups

Although, from the clinical and physiologic viewpoint, the 4 patients with ostium secundum defects and atrioventricular valve clefts resembled endocardial cushion defects very closely, the vectorcardiogram showed fundamental differences from the patterns just described in lesions of the endocardial cushion. The patterns, with the corresponding anatomic and physiologic data, are presented in figure 4. It may be seen that in the sagittal plane the body of the loop is principally inferior. Furthermore, the mean electrical axis in the frontal plane is to the right of 0°. The latter observation is of particular importance if regarded in the light of definite evidence of left ventricular hypertrophy in the frontal plane of patients c and d. This then suggests that the left axis deviation of patients with endocardial cushion defects is not exclusively—if at all—due to the presence of left ventricular hypertrophy.

The vectorcardiograms of the 2 patients with ventricular septal defect and tricuspid valve cleft, simulating endocardial cushion defects clinically and physiologically, are reproduced in figures 5 and 6. The patient without pulmonary artery hypertension (fig.

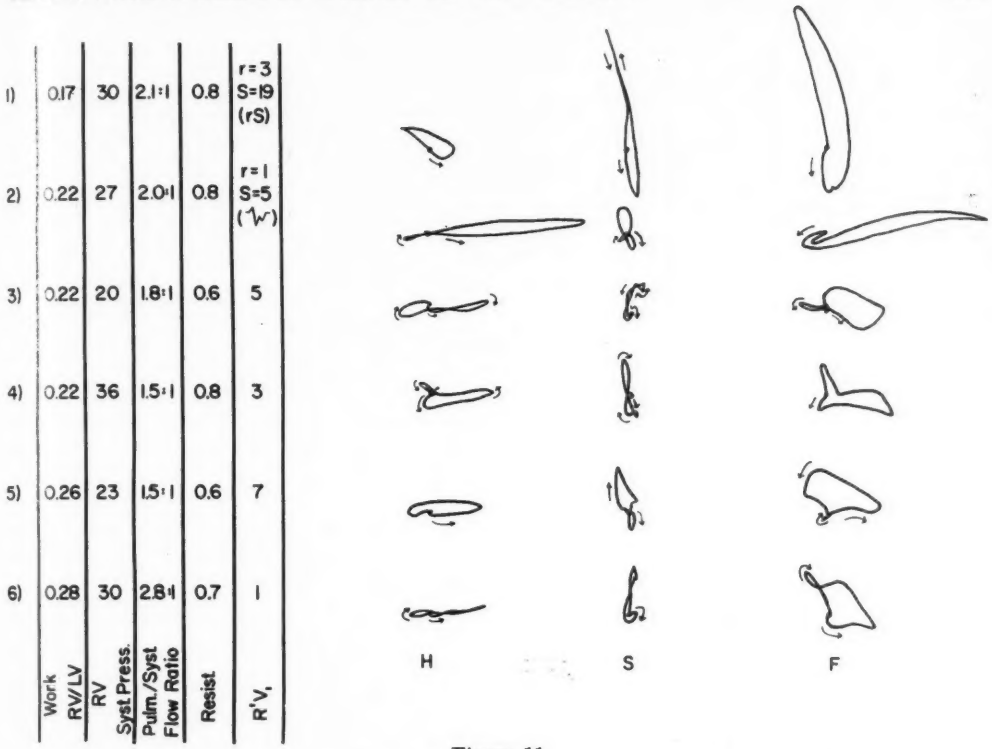

Figure 11

Scale drawings of the vectorcardiograms of patients (nos. 1-6) with endocardial cushion defects listed in order of increasing right ventricular/left ventricular work ratios. Hemodynamic data and the height of R′ in V_1 of the electrocardiogram are also included.

5) may be taken out of the entire group of atrial septal defects because of the lack of anterior and rightward forces. The vectorcardiogram of the second patient (fig. 6) at first glance resembles an ostium secundum loop. However, the counterclockwise inscription in the frontal plane in the face of marked right ventricular hypertrophy (as demonstrated in the horizontal and sagittal planes) makes the diagnosis untenable, since left ventricular hypertrophy is thus also present. It is assumed that the right ventricular hypertrophy is due to pulmonary hypertension.

Correlation of the Vectorcardiogram with Hemodynamic Data in Atrial Septal Defects of the Ostium Secundum and Endocardial Cushion Types

In view of the rather close relationship between hemodynamics and the electrocardiogram in pure pulmonic stenosis and aortic stenosis, the vectorcardiograms were related to the catheterization data. It was hoped the careful analysis of the measurements might permit valid conclusions about hemodynamics from the vectorcardiogram. It was also hoped that such an attempt at correlation would shed some light on the origin of the various patterns seen in the vectorcardiogram of atrial septal defects.

Figures 7 to 10 represent the hemodynamic data in 22 patients with ostium secundum lesions, with the corresponding vector loops drawn to scale. The patients are listed in order of increasing right ventricular/left ventricular work, the only measure that seemed to show significant correlation with the vectorcardiographic pattern. Neither the height of the R′ wave in V_1, nor the pulmonary arteriolar resistance, nor the pulmonary-

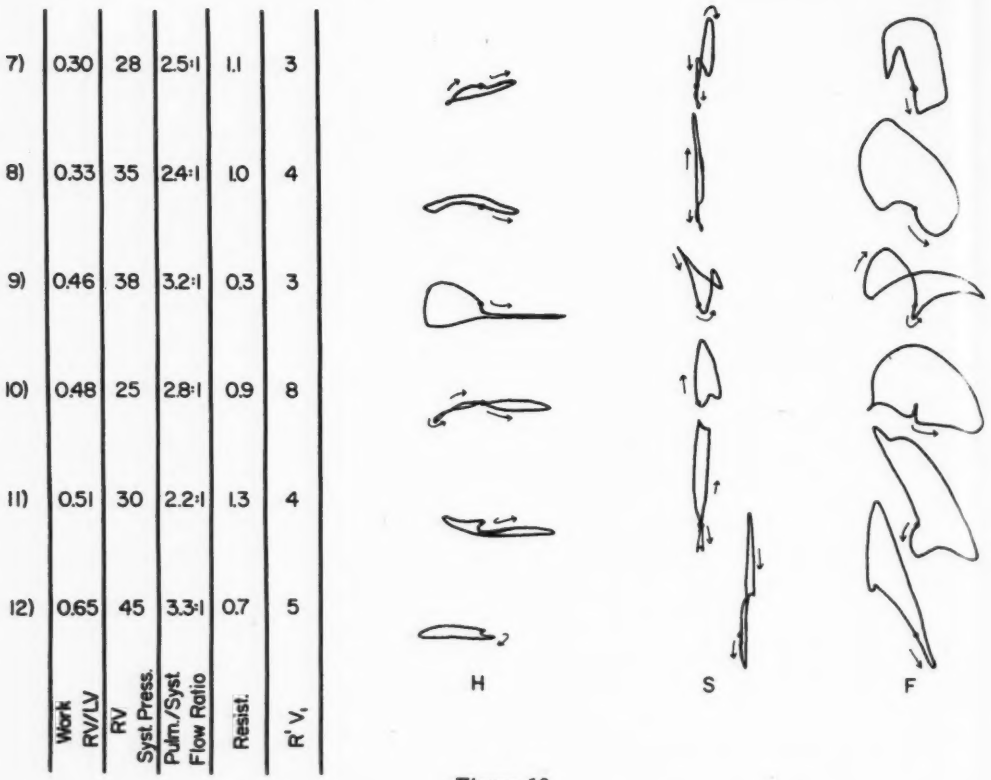

Figure 12

Scale drawings of the vectorcardiograms of patients (nos. 7-12) with endocardial cushion defects. (See legend for figure 11.)

systemic flow ratio could be related well with the vectorcardiogram, though right ventricular forces did seem to be influenced to a certain extent by the height of the right ventricular pressure.

In figure 7 it may be seen that the first 4 patients, though exhibiting right ventricular hypertrophy, do not have clockwise rotation in the body of the frontal plane. These patients all have work ratios of 0.4 or less. As the work ratio increases, clockwise rotation becomes more manifest and is missing only in 3 patients with conduction disturbances (patients 8, 14, 18).

The same correlation with increased right ventricular/left ventricular work is reflected in table 4. As the work ratio increases, the anterior and rightward forces also generally increase, especially so when considered in relation to the posterior and leftward forces. From the same table it can be seen that there is a complete lack of correlation between the mean electrical axis in the frontal plane and the work ratios or right ventricular hypertrophy.

Figures 11 to 14 represent the vectorcardiograms of 22 patients with endocardial cushion defects correlated with hemodynamic data. These loops are also grouped in order of increasing right ventricular/left ventricular work ratios, though we are fully cognizant that this may not be as valid a measurement in this group as it is in ostium secundum defects. The left ventricular work inherent in mitral regurgitation is obviously not measurable by our present-day technics, nor can the

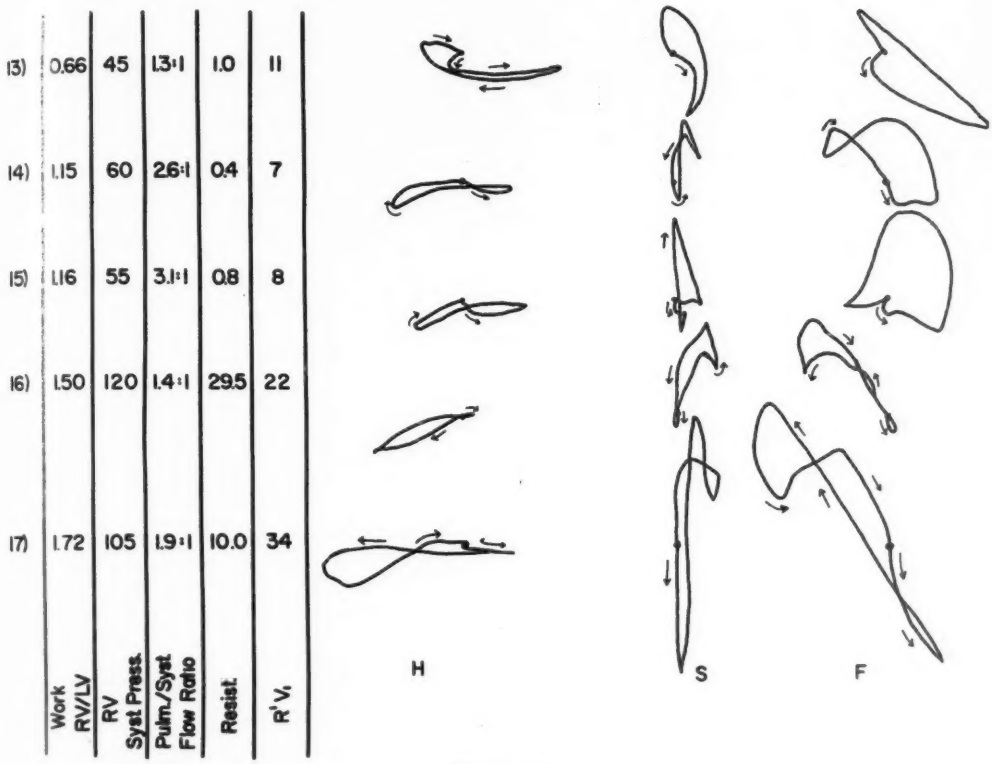

Figure 13

Scale drawings of the vectorcardiograms of patients (nos.13-17) with endocardial cushion defects. (See legend for figure 11.)

effect of tricuspid regurgitation on right ventricular work be accurately estimated.

Again, as in the ostium secundum group, only the work ratios seemed to influence in any consistent way the vector loops, and even this correlation, as expected, is less clear-cut than in the other group. The trend of increasing right ventricular forces with increasing work ratio is evident, however. In the sagittal plane it can be seen that more patients demonstrated a counterclockwise inscription as right ventricular work increased. Meanwhile, in the frontal plane, of the total of 22 patients, only 5 were not wholly counterclockwise, 4 of these having work ratios of 1.5 or more.

In table 5 we again see the general dominance of rightward and anterior forces with increasing right ventricular work, as well as the unreliability of the mean electrical axis as a measure of preponderance of the right or left ventricle.

Discussion

In discussing the vectorcardiogram of atrial septal defect, it may be worthwhile to consider the rsr′ pattern so characteristic of this congenital cardiac lesion. Barber et al.[9] maintained that 95 per cent of individuals with atrial septal defects have this pattern. Our experiences confirmed this in a previous publication,[10] as well as in the present study, in which a prominent rightward terminal force anterior enough to cause an r′ in V_1 of the electrocardiogram was seen in 54 of the 55 patients. Contrary opinion has been expressed by others.[11-13]

The significance of this rsr′ configuration

Table 5

Endocardial Cushion Defects (Vector Analysis versus Work Ratio)

Patient no.	Right	Anterior	Right/Left	Superior/ Inferior	Right + anterior— left + posterior*	Right + anterior/ left + posterior†	Frontal plane angle
1	0.26	0.10	1.1	2.8	—0.04	0.9	—75°
2	0.24	0.08	0.2	1.7	—1.32	0.2	—10°
3	0.28	0.14	0.5	1.0	—0.16	0.7	0°
4	0.10	0.12	0.2	1.8	—0.46	0.3	+10°
5	0.24	0.04	0.5	2.6	—0.34	0.5	—60°
6	0.22	0.04	0.5	1.4	—0.28	0.5	—35°
7	0.28	0.14	1.0	2.5	+0.10	1.3	—70°
8	0.48	0.04	1.3	3.0	+0.06	1.1	—95°
9	0.46	0.16	0.8	2.4	+0.02	1.0	—90°
10	0.42	0.16	0.7	2.4	—0.02	1.0	—60°
11	0.38	0.10	0.7	3.0	—0.14	0.8	—50°
12	0.52	0.10	3.7	3.5	+0.46	3.4	—110°
13	0.30	0.26	3.1	0.7	—0.50	0.5	+35°
14	0.60	0.22	1.3	2.6	+0.36	1.8	—75°
15	0.40	0.24	0.7	2.7	+0.06	1.1	—115°
16	0.80	0.34	8.0	9.0	+1.04	11.4	—130°
17	1.24	0.38	2.7	1.2	+1.14	3.4	—125°
18	0.66	0.80	1.1	2.6	+0.78	2.1	—85°
19	0.62	0.14	3.1	2.3	+0.44	2.4	—110°
20	1.14	0.34	7.3	1.3	+0.88	7.3	—175°
21	1.04	0.58	3.5	2.6	+1.30	5.4	—120°
22	0.54	0.28	5.4	2.9	+0.70	8.2	—115°

Patients listed in order of increasing severity of right ventricular/left ventricular work. Linear measurements are in millivolts. The exact work ratios can be found in figures 15-18.

*Calculated by adding the right plus anterior linear measurements and subtracting the sum of the left plus posterior measurements.

†Calculated by adding the right plus anterior linear measurements and dividing this sum by the sum of the left plus posterior measurements.

has been a subject of controversy. Grishman's group[14] stated that this pattern in patients with atrial septal defect means right ventricular hypertrophy. Richman and Wolff,[15, 16] on the other hand, indicated that it is an expression of right bundle-branch block, with coexisting right ventricular hypertrophy.

All but 1 of our 55 patients with atrial septal defect had right ventricular hypertrophy, fulfilling the criteria of Grishman. The 1 exception (patient 1 fig. 11) had a very low work ratio, top normal right ventricular pressure, a 2:1 left-to-right shunt, and no rsr′ pattern. The presence of right bundle-branch block—defined by Grishman as marked terminal slowing in all 3 planes of a rightward and anterior terminal appendage—was demonstrated in only 3 of our patients (2 ostium secundum lesions, 1 endocardial cushion defect). The conduction defect was diagnosed in 10 patients when Wolff's criteria were used—a prominent terminal appendage to the right, anterior and superior (inferior in horizontally positioned frontal plane loops) without the necessity of terminal slowing. Seven of these were ostium secundum lesions, while 3 were endocardial cushion defects.

Thus we believe that practically all patients with atrial septal defect have right ventricular hypertrophy. Whether or not right bundle-branch block is also present depends on the definition of the investigator, but by any definition available it is not a constant finding.

The differential diagnosis of the ostium secundum and endocardial cushion defects from an electrocardiographic viewpoint, has been amply discussed in the past.[17-20] Vectorcardiographic analysis of the problem has

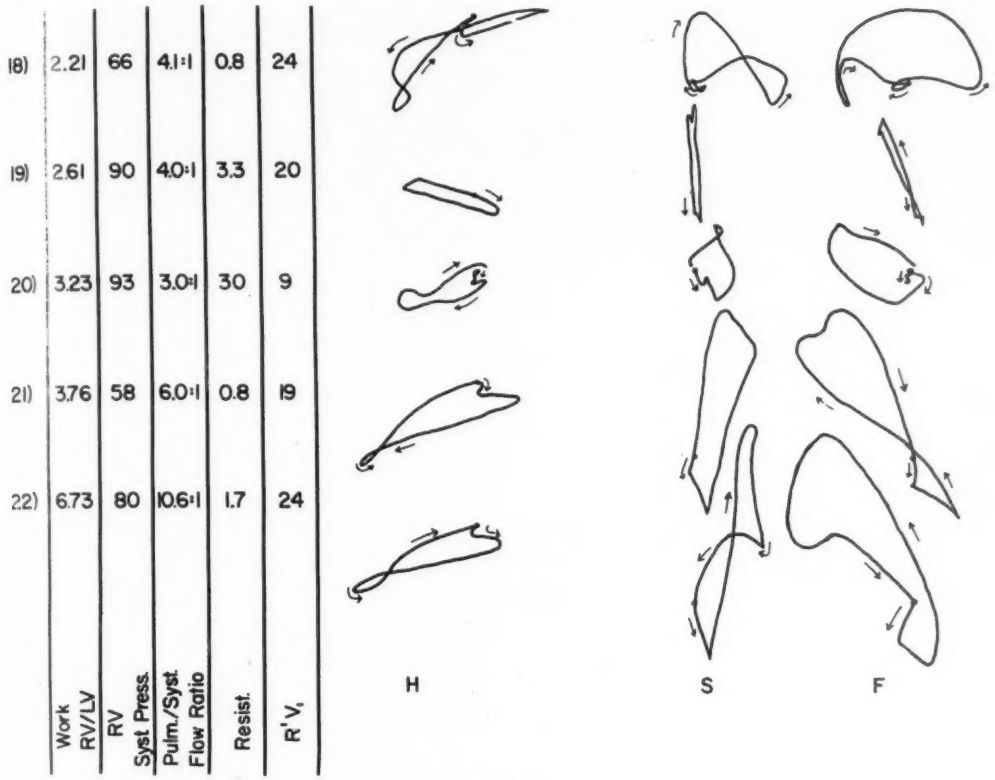

Figure 14

Scale drawings of the vectorcardiograms of patients (nos. 18-22) with endocardial cushion defects. (See legend for figure 11.)

been alluded to on the basis of our data,[17] and discussed by others.[19, 21] It seems clear from our results that the superior orientation in endocardial cushion defects provides a clear-cut differentiation from the inferior orientation of atrial septal defects of the secundum type. The negative mean electrical axis in the frontal plane of the former, together with the positive axis in the latter, serves similarly. These facets of conduction, of course, can be seen in the electrocardiogram in the frontal plane axis and in aV_F. An advantage of the vectorcardiogram is that it demonstrates the true axis in cases in which the mean electrical axis in the electrocardiogram appears perpendicular to the frontal plane. Furthermore, in individuals with equiphasic aV_F, the vector can tell us whether the superior or inferior loop is dominant and, of course, in which direction the loop is inscribed. The fact that ostium secundum lesions have frontal plane loops that are clockwise, while endocardial cushion defects give counterclockwise frontal plane vectors, can sometimes not be accurately derived from the electrocardiogram. When we considered the 4 patients with atrial septal defects of the secundum type plus atrioventricular valve clefts, and the 2 patients with ventricular septal defect plus tricuspid valve clefts, the vectorcardiogram was very effective in separating these unusual entities from the 2 major groups.

It may be said, thus, that the vectorcardio-

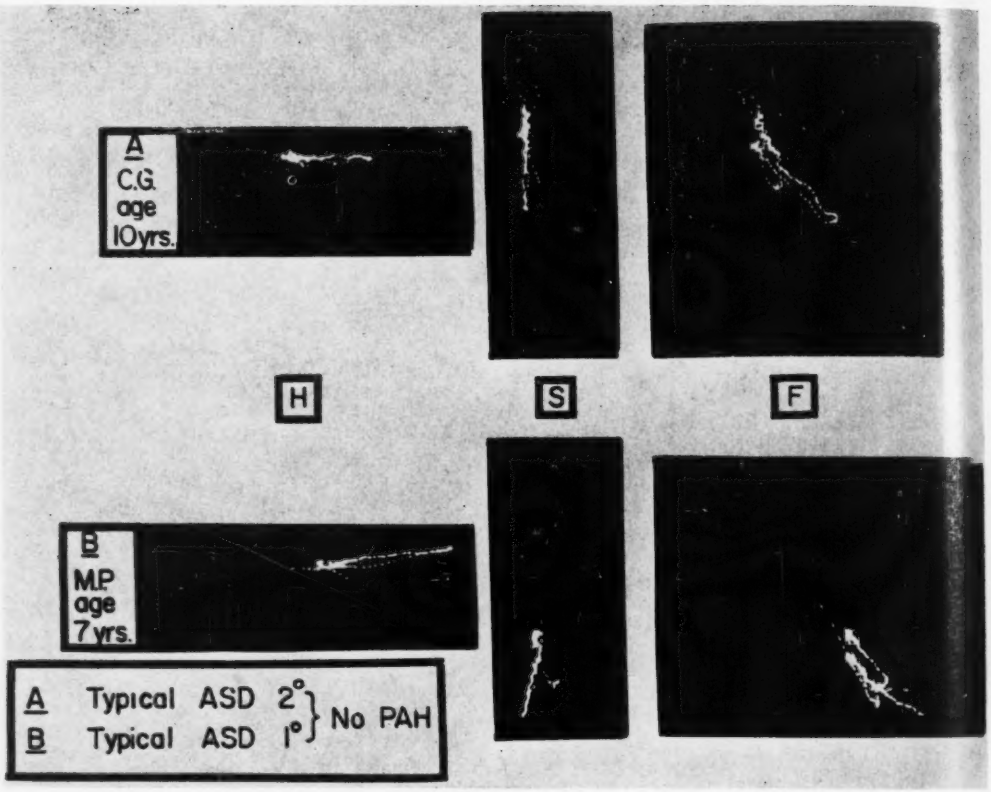

Figure 15

Typical ostium secundum (A) *and endocardial cushion* (B) *defects without pulmonary artery hypertension. Note that despite comparable degrees of right ventricular hypertrophy as manifested in the horizontal planes, the loops are inferior in the ostium secundum, superior in the endocardial cushion defect. In addition, the frontal plane inscription is clockwise in the ostium secundum, counterclockwise in the endocardial cushion defect.*

gram does not reveal anything more than does vectorial analysis of the electrocardiogram in terms of differentiating ostium secundums from endocardial cushion defects, except in occasional instances, but it may be helpful in differentiating unusual situations from the 2 major groups.

The origin of the superior forces and the left axis deviation secondary to it, as seen in endocardial cushion defects, has also been a matter of controversy. Blount and associates[22] suggested that left ventricular hypertrophy, secondary to mitral regurgitation, is the reason for the left axis deviation. They cited 1 patient with an ostium primum type of endocardial cushion defect without a mitral valve cleft, who had normal axis deviation (0 –+90°). Wakai and Edwards,[23] reviewing the photograph of the autopsy specimen, questioned the validity of the diagnosis of ostium primum, because the atrial defect was too far posterior in the atrial septum. Forest[24] also described a case of an endocardial cushion defect without left axis deviation. Reviewing the autopsy data, we think that his case is more likely to represent a ventricular septal defect with tricuspid regurgitation. Further evidence, denying that the origin of the left

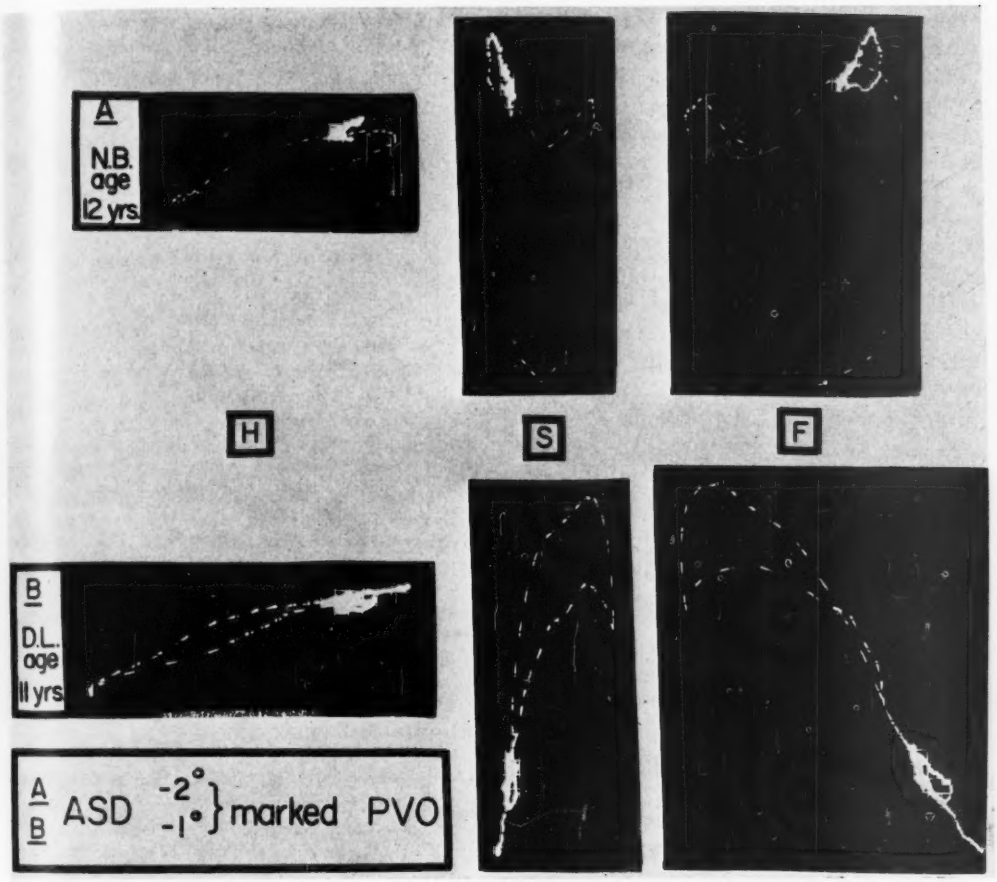

Figure 16

Ostium secundum (A) *and endocardial cushion* (B) *defects with marked pulmonary vascular obstruction. Note that despite maximal right ventricular hypertrophy in each, superior orientation remains in the endocardial cushion defect. Note also that the direction of inscription in the frontal plane of the endocardial cushion defect has become clockwise.*

axis deviation lies in the mitral regurgitation, is furnished by a case reported by Allen[25] of a patient with an ostium primum defect, no mitral valve cleft, and an electrocardiogram (courtesy Dr. E. Grey Dimond) of marked left axis deviation (−120°).

A more attractive hypothesis to explain the superiorly oriented vector has been suggested by Toscano-Barbozo.[19] This author believed that the left axis deviation in endocardial cushion defects is the result of a fundamental alteration in excitation pathways into the ventricles. Our data also seem to indicate that the superior loop is not due to left ventricular hypertrophy secondary to mitral regurgitation. Ostium secundum defects with mitral valve clefts may have appreciable left ventricular hypertrophy without left axis deviation (fig. 4). Furthermore, figures 15 and 16 demonstrate that ostium secundum defects have inferior loops whereas endocardial cushion defects have superior loops,

despite comparable degrees of right ventricular hypertrophy, as demonstrated in the horizontal plane. It is noteworthy that the vector loop of the patient with an endocardial cushion defect and severe pulmonary vascular obstruction is clockwise in the frontal plane, the last vestige of evidence of left ventricular hypertrophy thus being lost—and still the superior loop remains!

When the relationship between hemodynamic data and the vectorcardiogram was analyzed, we were impressed by the substantially better correlation between the vector loop and the work ratio than with any other measure. This may prove to be a fruitful avenue for further investigation. It may also further point to the vectorcardiogram being a somewhat more useful tool than is the electrocardiogram in the understanding of these cases.

Summary

Vectorcardiograms have been analyzed in 32 atrial septal defects of the secundum type and 23 endocardial cushion defects, as well as 6 patients in special groups.

All but 1 patient in both major groups showed right ventricular hypertrophy, with clear-cut evidence of additional right bundle-branch block being present in only 3.

The principal difference between ostium secundum and endocardial cushion defects consists in the loop being inferior in the former, superior in the latter. The direction of inscription in the frontal plane tends to be clockwise in the ostium secundum lesions, counterclockwise in the endocardial cushion group.

The 6 patients in special groups could be readily distinguished from the 2 major groups with the use of the vectorcardiogram.

The superior position of the vector loop (left axis deviation in the electrocardiogram) characteristic of endocardial cushion defects, is thought not to be secondary to left ventricular hypertrophy but rather to a congenital anomaly in the conduction system.

A correlation was attempted between the vectorcardiogram and hemodynamic data in 22 patients in each group. The ratio of right to left ventricular work appeared to relate well to the vectorcardiogram. As the ratio increased, more right ventricular hypertrophy appeared.

Acknowledgment

We wish to express our appreciation to Dr. Eliot Young, for helpful suggestions and criticism, to Dr. Abraham Rudolph in whose laboratory the cardiac catheterizations were performed, and to Miss Sarah Duncan and Mrs. Mary Peterson, who helped in the laborious work of making the prints for publication.

Summario in Interlingua

Esseva analysate le vectorcardiogrammas in 32 casos de defecto atrio-septal del typo de ostio secunde, 23 casos de defecto de cossino endocardial, e 6 casos de patientes in gruppos special.

Omne le patientes, con le exception de 1 in cata un del duo major gruppos, monstrava hypertrophia dextero-ventricular, con evidentia clar del presentia additional de bloco de branca dextere in solmente 3.

Le differentia principal inter defecto de ostio secunde e defecto de cossino endocardial consiste in le facto que le ansa es inferior in le prime e superior in le secunde. Le direction del inscription in le plano frontal exhibi un tendentia dextrorse in le lesiones de ostio secunde e sinistrorse in le lesiones de cossino endocardial.

Le 6 patientes in gruppos special esseva facilemente distinguibile ab le 2 gruppos major per medio del vectocardiogramma.

Es opinate que le position superior del ansa (deviation sinistrorse del axe in le electrocardiogramma) que es characteristic de defectos de cossino endocardial non es secundari a hypertrophia sinistro-ventricular sed plus tosto a un anomalia congenite in le systema de conduction.

Esseva facite le tentativa de correlationar le vectocardiogramma con datos hemodynamic in 22 patientes in cata un del duo gruppos. Le proportion de travalio ventricular dextere a sinistre pareva esser ben relationate al vectocardiogramma. In tanto que ille proportion cresceva, plus marcate grados de hypertrophia ventricular se manifestava.

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It is hardly necessary to mention a humble attitude as a qualification of the man of science. How little we know of the immensity and structure of the universe and of the nature of the earth and all who dwell therein! How meager, during the days of his years, can be the contributions of any investigator toward the solution of the endless mysteries!—WALTER B. CANNON, M.D. *The Way of an Investigator.* New York, W. W. Norton & Co., Inc., 1945, p. 42.

A Double-Needle Technic for Transbronchial Left Heart Catheterization

By STEWART M. SCOTT, M.D., ROBERT G. FISH, M.D., AND TIMOTHY TAKARO, M.D.

CONTINUING progress in the surgical management of rheumatic mitral vascular disease makes accurate preoperative appraisal of mitral valvular function mandatory. Left heart catheterization studies have therefore become essential in many cases. Unlike the posterior transthoracic approach to the left side of the heart, transbronchial left heart catheterization has been limited to a single-needle technic. Although Colvez et al.[1] have described a single-needle method for recording simultaneous left atrial and ventricular pressure pulses, we have felt that if a second needle could be safely introduced into the left atrium by the transbronchial route, more accurate as well as additional studies could be obtained. This has led to a modification of the standard Morrow transbronchial needle[2] and a modification of the technic of transbronchial left heart catheterization which is described.

Description of Needle and Technic

The original Morrow needle has been modified by attaching 6 metal guides to the left side of the shaft (fig. 1). An accessory 18-gage thin-walled needle, 55 cm. long, is inserted through these guides. The guides were constructed so that the accessory needle and the Morrow needle are parallel but 4 mm. apart at their distal ends. The entire assembly passes easily through a standard 8-mm. Broyles bronchoscope. The depth to which the accessory needle is inserted into the left atrium is limited to the same depth as the Morrow needle by a needle stop that impinges against the bronchoscope.

Initially a polyvinyl catheter is placed in the ascending aorta by means of percutaneous, retrograde catheterization of the right brachial artery. The Morrow needle is then passed transbronchially into the left atrium with the accessory needle in the withdrawn position. After left atrial pressure has been recorded, a polyethylene or polyvinyl catheter is passed into the left ventricle through the Morrow needle. Once satisfactory positioning of this catheter is obtained, the accessory needle is inserted into the left atrium, being automatically directed by the metal guides. Simultaneous atrial, ventricular, and central aortic pressure pulses are recorded. The blue-dye test for mitral insufficiency as described by Fisher[3] is then performed. Upon withdrawal of the catheter from the ventricle to the atrium for completion of the blue-dye test a pull-through is recorded (fig. 2). Finally both needles are removed and the tracheobronchial tree is thoroughly aspirated of blood. The average time of endoscopy is 30 minutes. Cardiac output is determined by catheterization of the pulmonary artery and utilization of the Fick principle.

Results

Twenty left heart catheterizations have been performed by this technic without complications. The second needle was easily inserted into the left atrium in every instance. The amount of bronchial bleeding encountered has not been excessive.

Discussion

The transbronchial technic of left heart catheterization has been shown to be a safe and reliable procedure.[2, 4] This method of studying function of the mitral valve has usually been limited to recordings through a single lumen with sequential pressure tracings across the valve. To avoid the inconvenience of later superimposition of these pressure pulse tracings and to determine more accurately the left ventricular filling gradient in the presence of stenotic lesions, simultaneous tracings are necessary.

Modification of the Morrow needle now permits simultaneous placement of 2 needles into the left atrium. The second needle is not inserted until the left ventricle has been successfully catheterized. Simultaneous and equisensitive left ventricular and left atrial pressure pulses may then be obtained and superimposed by means of a photographic

From the Cardiopulmonary Laboratory, Veterans Administration Hospital, Oteen, North Carolina.

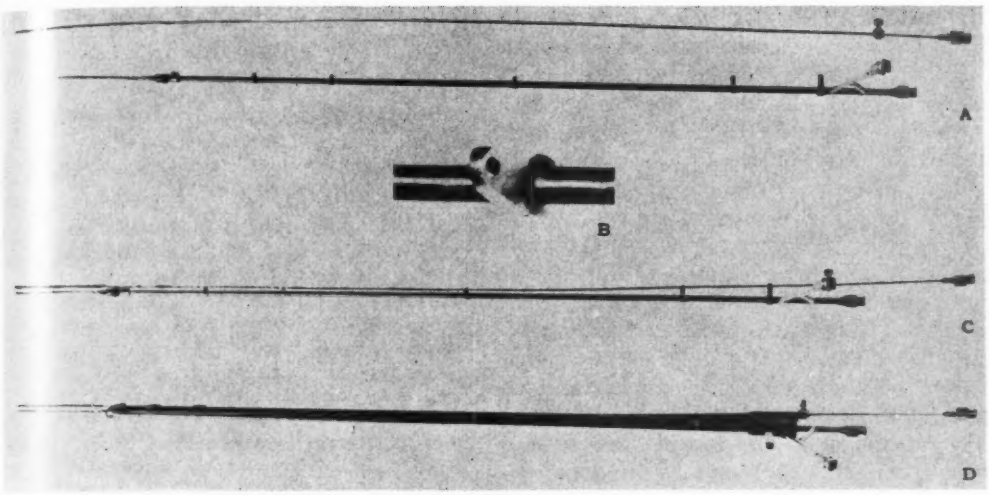

Figure 1

A. Disassembled view showing the 18-gage, thin-wall, accessory needle, 55 cm. long, with needle-stop attached near the hub, and the modified Morrow needle with attached metal guides. B. Enlarged view of metal guide attached to Morrow needle. C. Morrow needle and accessory needle assembled. The accessory needle has been advanced to the same depth as the Morrow needle. D. Two needles within a standard 8-mm. Broyles bronchoscope. The needle-stop is shown impinging against the edge of the bronchoscope.

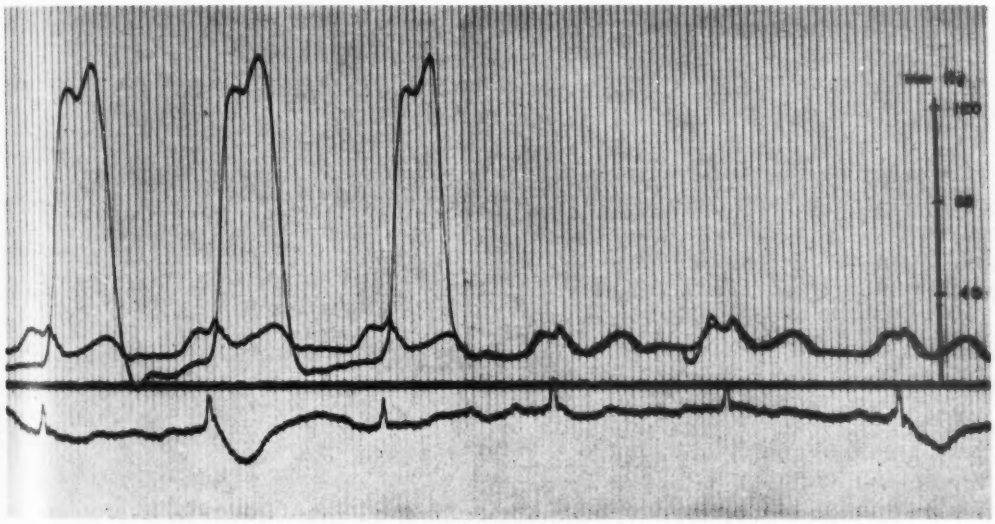

Figure 2

Simultaneous left ventricular and left atrial pressures. The ventricular pressure is recorded from a polyethylene catheter passed through the Morrow needle, while the atrial pressure is recorded from the accessory atrial needle. Withdrawal of the catheter across the mitral valve reveals the accurate conformity of the catheter and needle recordings.

recorder. This permits more accurate measurement of a ventricular filling gradient and calculation of valve area from a modification of Gorlin's original hydraulic formulae.[5]

In evaluating mixed mitral valvular lesions it is desirable to supplement pressure studies with a dye test for mitral insufficiency, which can be performed in the average laboratory. The complexities of instrumentation, recording, and interpretation make widespread utilization of the various radioisotope and peripheral arterial dye-dilution technics impractical at the present time. The Fisher blue-dye method for assessing the severity of mitral insufficiency is simple, however, and is easily adaptable to the 2-needle technic described. Although one may question the validity of this test primarily on the basis of the adequacy of atrial mixing, from a practical standpoint it has aided materially in selection of patients for surgery.

The freedom from complications in this series, coupled with the experience of others[3] in multiple punctures of the left atrium, makes us believe that this is a safe and useful procedure.

Conclusions

The Morrow needle for transbronchial left heart catheterization has been modified to permit the insertion of 2 needles into the left atrium. A safe and reliable 2-needle technic for transbronchial left heart catheterization is described. Since this permits simultaneous left ventricular and left atrial pressure pulse recordings and performance of blue-dye studies by Fisher's technic, a more accurate and complete appraisal of mitral valvular function is possible. This technic has been applied in 20 consecutive left heart catheterizations without complication.

Acknowledgment

We wish to acknowledge the assistance of A. W. Chattaway, of the Asheville Tool and Gauge Company, Asheville, North Carolina, in the construction of the modified Morrow needle described.

Summario in Interlingua

Le agulia de Morrow pro catheterismo sinistro-cardiac transbronchial esseva modificate de maniera a render possibile le introduction de 2 agulias in le atrio sinistre. Un salve e fidel technica a 2 agulias pro catheterismo sinistro-cardiac transbronchial es describite. Proque isto permitte le simultanee registration de pulsos de pression sinistro-ventricular e sinistro-atrial con le effectuation de studios a tinecturation blau secundo le technica de Fisher, un plus accurate e complete evalutation del function del valvula mitral deveni possibile. Iste technica esseva applicate in 20 consecutive catheterisationes sinistro-cardiac sin ulle complication.

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Thus we are men, and we know not how: there is something in us that can be without us, and will be after us; though it is strange that it hath no history what it was before us, nor cannot tell how it entered in us.—Sir Thomas Browne. *Religio Medici.* Edited by W. A. Greenhill, M.D. London, MacMillan and Co., Ltd., 1950, p. 60.

SYMPOSIUM ON CORONARY HEART DISEASE

Diagnosis of Angina Pectoris

By E. Cowles Andrus, M.D.

THE MYOCARDIUM is to a critical degree dependent upon its contemporary blood supply. In contrast to skeletal muscle, which can perform work beyond the capacity of its aerobic metabolism to support, thus acquiring an oxygen debt and repaying it later, heart muscle continuously requires oxygen supply and irrigating blood sufficient for its immediate demands. Replenishment of its energy stores and removal of metabolites must literally be accomplished between beats. The rate of oxygen extraction from blood in the coronary system is correspondingly high, the difference between arterial and venous blood being 60 to 70 per cent, and, even when the heart beat is arrested, myocardial oxygen consumption is measurably greater than that of skeletal muscle. Under such circumstances, obviously, increased demand for oxygen can be met only by increased rate of blood flow. In the normal heart, this is amply provided for, but with aging or disease it may be compromised. With aging, the arterial walls become stiffened, and with disease, notably atherosclerosis, increased coronary flow may be impeded to a serious degree. Despite the development of some collateral anastomoses with other, more fully patent, coronary vessels, blood supply may become insufficient over large or multiple areas of the myocardium when generalized coronary arterial changes limit the maximum increase upon demand, or locally when changes in a single artery or its branches obstruct the flow in the domain of that vessel.

Since coronary artery disease and coronary insufficiency—by whatever name—were first recognized as cause and effect, there has existed a compelling urge to confirm the diagnosis and to gain some hint regarding prognosis by objective means. When the myocardium has suffered manifest injury in the process, this may not be difficult; but pain as the principal, and sometimes the only, symptom eludes even the most modern recording devices.

Thus it is that 188 years after Heberden the most rewarding procedure in the diagnosis of angina pectoris is still an unhurried interview with the patient. Indeed, his own account of his distress, its distribution, and the circumstances under which it appears or subsides establishes the diagnosis in the vast majority of cases.

The pain or distress is described as "squeezing, choking, pressing, aching, or burning," rarely as sharp or stabbing. It increases gradually to its maximum intensity, persists for a few minutes and then subsides, usually more rapidly than it develops. In describing his symptoms the patient so frequently presses his hand upon the sternum or clenches his fist before his chest that these gestures almost attain the stature of a sign of angina pectoris. Pain characteristically begins in the midline behind the sternum, usually its upper two thirds. It may be confined to that location and, if so, may be confused with pain of esophageal spasm or disease. The latter tends, however, to wax and wane, to penetrate to the midline in back, and to be influenced by swallowing. Anginal pain tends to spread symmetrically to areas near the sternum but then commonly extends over the upper pectoral region, to the neck, to the front of the

From the Cardiovascular Division of the Department of Medicine, Johns Hopkins University, Baltimore, Md.

shoulders, and down the medial aspect of the arms to the wrists and hands, particularly on the ulnar side. The spread of pain usually involves the left side more than the right, and may appear in hands, wrists, and arms alone, where the quality of this sensation is often described as aching or tingling. Uncommonly, pain spreads to the jaw, again more frequently on the left, to teeth, to the face, or to the suprascapular area; rarely the pain may commence there.

Equally significant to the diagnosis are the conditions provoking the pain, and the circumstances under which it subsides. It characteristically appears under stress—exertion, anger, "aggravation," or excitement—and it abates promptly (in a matter of minutes) with rest or under the effect of nitroglycerin. The effect of any or all of these inciting causes is evidently potentiated after a meal, which may in itself call forth a 25 per cent increase in cardiac output, by a cold environment, or during a state of anxiety.

Obviously pain or distress in the areas and structures just mentioned may not be due to angina pectoris. With acute pericarditis, precordial pain may be present and intense; it is, however, usually constant, often affected by the position of the patient or by deep breathing, and not significantly influenced by effort. Anxiety is accompanied by a sense of "weight on the chest." Patients with neurocirculatory asthenia complain of "heartache" or stabbing pain, usually not in the midline but over the lower precordium and the region of the cardiac apex. Postural strain can provoke spasm and aching in the pectoral muscles, usually accompanied by tenderness on pressure or pain on stretching. Periarthritis of the shoulder may be associated with pain confusingly similar to that of angina pectoris but commonly located on top of the shoulder or behind it, extending down on the outside of the arm, accompanied by restriction of motion, and intensified by rotating movements of the shoulder joint. Unhappily this condition may result from prior myocardial infarction and may mask the pain of genuine angina pectoris. The patience and ingenuity of the examiner may be taxed to obtain an exact and detailed story of the patient's symptoms in such cases, but even here the history is the foundation of the diagnosis; the most important clue, when it can be elicited, is the inciting relationship between exertion or excitement, particularly after eating, and the onset of pain.

Far more difficult to evaluate is pain or discomfort typical of angina pectoris in quality and distribution but coming on when the patient is quiet, at rest, at the *beginning* of a meal (rather than after it, during digestion) or even in bed, when it may wake him from sleep. To this latter type of attack the term *angina pectoris decubitus* has been applied, and in some cases, its inciting cause has been presumed to be the increased return to the heart during recumbency of blood that had pooled in venous reservoirs, e.g., in the abdomen, while the patient was upright during the day. Some support may be found for this thesis in the fact that some persons so afflicted lose their nocturnal pain after full doses of digitalis or by sleeping upon a slanted bed with its head a few inches higher than its foot. But it frequently appears that these and some of the other examples of angina pectoris at rest mentioned above may be set off by visceral reflexes conveyed via the vagus from esophagus (entrapped hiatus hernia), stomach,[1] or diseased gallbladder.[2] Presumably the effect of such reflexes is to diminish coronary flow by inducing coronary constriction. Probably this is significant only when superimposed upon the consequences of coronary disease. The effect of adequate doses of atropine may be dramatically helpful in diagnosis.

In any event, accurate appraisal of these symptoms is especially urgent in that such pain, and particularly the setting in which it occurs, has much in common with manifestations of imminent myocardial infarction. Indeed pain in this pattern, occurring with increasing frequency and intensity, is a well-recognized warning of progressive coronary occlusion.

When a history suggests angina pectoris,

some confirmation may be gained by discovering conditions—hypertension or cardiac hypertrophy, aortic stenosis or regurgitation—that would contribute to the development of coronary insufficiency. When observed during an attack of angina pectoris, however, the patient may display no objective change from his previous status beyond pallor and sweating. Commonly the blood pressure rises while pain is present, or transient signs of left ventricular failure (pulmonary congestion or Gallop Rhythm) may be detected and frequent extrasystoles or other arrhythmia may sometimes appear.

Electrocardiography

Abnormalities in the electrocardiogram recorded at rest and in the absence of pain may add to the examiner's suspicion that a patient suffers from angina pectoris insofar as these may indicate prior myocardial damage. In the large majority of instances the diagnosis can be made without resort to electrocardiography but in doubtful cases it is often helpful. Under such circumstances no effort should be spared to obtain a record during an attack. After careful questioning one should try to reproduce the circumstances that regularly provoke distress, such as exercise after a meal, or, if necessary, send the electrocardiographer to the patient to obtain a record during his daily activity.

Failing this, one may resort to one of the more or less standardized stress tests, such as exercise or induced hypoxemia, which may provoke the characteristic attack or engender changes in the electrocardiogram. In the writer's experience this is necessary in well under 10 per cent of cases. Properly and carefully conducted, these tests are not hazardous but no patient should be subjected to such stress whose electrocardiogram taken at rest immediately prior to the test is already indicative of myocardial ischemia. Moreover, patients who show conspicuous electrocardiographic changes after stress should be reexamined on the next day with another record at rest.

It is the aim of stress tests as applied to patients with suspected disease of the coronary arteries to disclose evidence of relative deficiency of myocardial blood supply. The usefulness of such procedures, indeed their validity, depends upon their ability to distinguish abnormalities from variations in the electrocardiogram that appear after stress in the absence of significant disease. Except for the unusual instance in which bundle-branch block develops following exercise or hypoxemia, the meaningful electrocardiographic changes, indicating myocardial ischemia, involve the S-T segments. It is precisely here that the electrocardiogram as recorded in practice is subject to variations in form that are not necessarily due to disease. Take, for example, deviation of the S-T takeoff. Certainly in the conventional limb leads the QRS complex, unless widened, is recorded before the atrial action current is completed; the Ta wave, even when shortened during tachycardia, lasts measurably beyond the end of QRS. Moreover, with increase in heart rate the Ta wave may increase in amplitude, causing depression of the S-T takeoff in a complex following an upright P wave. Error in interpretation of such an effect may be avoided by comparing the level of S-T junction with that of the P-Q segment and the QRS complex. Fortunately, too, the influence of the Ta wave on S-T deviation is minimal in the lateral chest leads, where the effects of ischemia on the electrocardiogram are most obvious.

A second effect of increased heart rate upon the S-T segment in the absence of disease involves the difference in rate of repolarization in the inner and outer layers of ventricular muscle with consequent change in the ventricular gradient. When rate of recovery after excitation is relatively more affected by tachycardia in the inner portions of the muscle than in the outer, the consequent changes in the conventional electrocardiogram may involve deviations of the S-T segment that approximate in degree those which result from deep myocardial ischemia.

In the patient with coronary artery disease stress may have all the electrocardiographic consequences of tachycardia mentioned above

and in addition may bring to light changes characteristic of relative insufficiency of myocardial blood supply. When myocardial ischemia is generalized or presumably when it involves multiple discontinuous areas, the electrocardiogram may be strikingly altered even in the remote (limb) leads.

Since such changes in the electrocardiogram after stress have so much in common with those that accompany tachycardia, it is no wonder that definition of positive and negative results of stress tests has met with some difficulties. Our own experience has been almost entirely confined to the 2-step exercise test of Master and Oppenheimer.[3,4] We regard the following changes, if they appear after standard exercise, as indicating coronary insufficiency:

1. S-T deviation of 1.5 mm. or more with flattened or downward-sloping S-T segment in the limb leads or lateral chest levels (over the left ventricle).

2. Inverted or diphasic T wave in leads I or II or lateral chest leads.

3. The development of bundle-branch block or the appearance of frequent extrasystoles.

Equally useful results are reported by those who employ the anoxemia test. This has the advantage that conditions may be perhaps more precisely controlled and distress can often be promptly relieved by administering 100 per cent oxygen. It has the disadvantage of requiring special equipment. Perhaps for this reason it has not been so widely applied and the standards for a positive test are less generally understood. These have, however, been described in detail by Levy and his colleagues[5] and have been reviewed by Stewart and Carr[6] and by Burchell, Pruitt, and Barnes.[7]

The significant changes in the electrocardiogram may not follow immediately after stress but may appear and progress during a period of from 1 to 15 minutes after exercise. The availability of direct-writing electrocardiographs has made it possible to "monitor" this reaction; in some instances important information may be gained by an almost continuous record. Since all leads may not be simultaneously recorded as a routine, it is pertinent to emphasize that the chest leads selected to follow the results of stress should be placed well out over the left ventricle. This may or may not be in the conventional position of lead V_4.

Some difficulty and confusion regarding the significance of the electrocardiographic response to stress may be avoided if certain facts are recognized. The result of a given test is diagnostically useful only if it is unequivocally positive, in which event, like angina pectoris, itself, it is indicative of severe localized or multilocular myocardial ischemia; it has no place as a means of "ruling out" coronary artery disease or angina pectoris. It testifies only to the contemporary status of the coronary circulation and except when extreme S-T deviation follows stress, it is not yet possible to attach quantitative significance to the degree of abnormality produced.

Perhaps as the natural history of coronary artery disease is more fully disclosed by careful follow-up studies, stress tests may acquire more prognostic value. There are such indications in reports of Mattingly, Robb, and their colleagues[8] showing significantly greater mortality rate at the end of 10 years and higher incidence of subsequent first coronary occlusion in persons with positive electrocardiographic reactions to stress. But it is still unwarranted in many cases, and in some instances certainly unwise, to reason in this respect from the general to the particular, from the statistical to the individual. The result of the stress test is simply another datum to be used by the patient's physician against the background of his history, symptoms, and physical signs.

Ballistocardiography

Ballistocardiography as a technic for detecting coronary artery disease or predicting its overt consequences is still in an evolutionary stage. Thanks to the ingenious and critical studies of Starr[9,10] and his collaborators it seems established that the ballistocardiogram describes primarily the functional state of the circulation and reflects, though it may not precisely record, the changes in pressure and

acceleration of blood flow that accompany the heart beat. The method as a diagnostic tool, however, is currently beset with important limitations. There have been serious difficulties in obtaining comparable records by different methods that accurately describe the force of cardiac contraction undistorted by other factors, such as the elastic properties of the body, deficient coupling with the ballistocardiograph, and the mechanical properties of the machine itself. The effect of the latter factor is evidently minimal in the "ultra-low frequency" method.

The interpretation of the ballistocardiogram has so far depended principally upon empirical correlation with clinical states otherwise defined rather than upon controlled physiologic experiments. In view, however, of the potential promise of this method, its limitations are under vigorous attack and certain conclusions regarding the utility of the technic have emerged. These have recently been summarized by Scarborough[11] as follows:

"The importance of ballistocardiography in the diagnosis and management of coronary heart disease is still an unsettled, and rather controversial, matter. There is no question that the ballistocardiogram is abnormal in a high proportion (about 80 per cent of all ages) of patients with this condition.[12] The limitation of the method in the diagnosis of coronary disease stems from the fact, ... , that . . . . abnormal ballistocardiograms are not infrequent among normal persons. In both groups the abnormality is of the nonspecific variety and both show similar progressive increases in frequency of abnormality with age. The nature of these relationships is such that the most significant findings are abnormal records from young persons and normal records from older ones. A variety of stress procedures has been used in conjunction with the ballistocardiograph and these have improved somewhat the discrimination between subjects with and without coronary disease.[13] . . . . the 'cigarette test'[14-16] has proved the most useful of these procedures but it is not without its drawbacks. When the control ballistocardiogram is abnormal, as it usually is in patients with coronary disease, it is sometimes difficult to determine whether it has become significantly more abnormal after smoking. Exercise is a more physiologically normal form of stress but it is technically difficult to obtain artifact-free ballistocardiograms during the period immediately after exercise. The intravenous injection of ergonovine in conjunction with ballistocardiography may prove useful diagnostically but experience thus far has been too limited to be sure; the same may be said of sublingual nicotine. It should be appreciated that the major source of difficulty in differentiating objectively between normal subjects and patients with coronary disease arises from our uncertainty as to whether the 'apparently' normal subjects are, in fact, free of coronary disease. Indeed, other evidence indicates that there is a substantial amount of coronary atherosclerosis in asymptomatic individuals over the age of 40. . . . A solution to the problem could be provided if it were shown that the individuals in the normal group whose control ballistocardiograms were abnormal or whose stress tests were positive subsequently developed coronary disease earlier or more frequently than did the remainder of the individuals."

Long-term studies are now in progress and the results do indeed suggest that the development of manifest coronary disease is more frequent in "normal" persons with abnormal ballistocardiograms than in those with normal records.[17, 18] Moreover, certain other observations stimulate interest in the possible utility of this method. It has been frequently noted that a patient's ballistocardiographic record deteriorates during an attack of angina pectoris and improves as the symptoms subside with rest or after nitroglycerin. Definite and sometimes striking improvement of the ballistocardiogram has been demonstrated in patients with overt coronary disease treated with low-fat diets.[19, 20] or estrogen preparations.[21] More studies of this sort should be particularly rewarding, since, as Scarborough points out, each patient serves as his own control and extracardiac factors such as aortic inelasticity are unlikely to change significantly over short intervals.

As far as the ballistocardiogram is concerned, therefore, it can serve to provide additional data regarding the likelihood of coronary disease, if it is abnormal at rest or after exercise or smoking in a patient under 40 years of age or if the record deteriorates during an attack of pain.

Summary

No technic or procedure yet devised surpasses the carefully taken clinical history in the diagnosis of angina pectoris. The electrocardiogram recorded during an attack, occur-

ring with the patient's ordinary activity or, in the few instances in which it is indicated, after standard exercise, is particularly helpful. The ballistocardiogram, though of suggestive value in some instances, has not yet achieved that degree of correlation with clinical findings to be uniformly valuable as a diagnostic tool, in view of the progressive increase in the proportion of abnormal records in the years beyond 40.

The fact remains that the incidence of severe coronary atherosclerosis is so high, particularly among men 45 years of age and older, as to demand continual effort to differentiate angina pectoris from other types of chest discomfort, to detect its earliest manifestations, or even to search out some refinement of diagnostic technic that may predict the consequences of coronary artery disease before coronary insufficiency has supervened.

Summario in Interlingua

In le diagnose de angina de pectore, nulle technica e nulle methodo ha essite trovate usque al presente le qual poterea esser reguardate como superior al meticulose scrutinio del antecedentes clinic del subjecto in question. Le electrocardiogramma obtenite durante un attacco que occurre in le curso del activitate ordinari del patiente o alora, in le casos in que isto es indicate, le electrocardiogramma obtenite post exercitio standard se monstra particularmente utile. Le ballistocardiogramma, ben que de valor suggestive in certe casos, ha non ancora attingite le grado de correlation con le constatationes clinic que esserea necessari pro render lo uniformemente utile como methodo diagnostic. In patientes de plus que 40 annos de etate, le registrationes ballistocardiographic include un crescente proportion de curvas anormal.

Le facto remane que le incidentia de sever atherosclerose coronari es si alte—particularmente inter masculos de 45 annos e plus de etate—que le continue effortio es requirite de differentiar angina de pectore ab altere formas de disconforto thoracic, de deteger su plus precoce manifestationes, o mesmo de elaborar le un o le altere raffinamento de technica diagnostic que permitterea le prediction del consequentias de morbo de arteria coronari ante que insufficientia coronari se ha declarate.

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Exercise Tests in the Diagnosis of Coronary Heart Disease

By EUGENE LEPESCHKIN, M.D.

THE DIAGNOSIS of coronary stenosis can be made easily from the history alone if typical symptoms of angina pectoris are present. When these symptoms are atypical, however, the diagnosis is more difficult. For instance, pleural or pericardial irritation, intercostal neuralgia or sternal or humeral bursitis may be aggravated by exercise, and spastic pain from the gastrointestinal tract may be also partly relieved by nitroglycerin.[1-4] If the patient happens to know the typical subjective complaints of angina, he may consciously or unconsciously shape his own symptoms to resemble them. On the other hand, true angina may sometimes be characterized by a completely atypical localization of the pain.

We know now that true angina is caused by insufficient blood supply to the heart, and this insufficiency should also affect the heart muscle and be reflected in the electrocardiogram. If the resting electrocardiogram shows definite signs of acute coronary insufficiency, no further tests are needed to confirm the clinical diagnosis. If the electrocardiogram is within normal limits, however, or shows changes that can be explained by other factors than coronary stenosis, it becomes necessary to wait for a spontaneous anginal attack, or to submit the patient to the conditions that usually provoke his anginal complaints to see whether a deficiency of the coronary circulation then becomes apparent. These conditions act usually by increasing the work of the heart and its oxygen consumption until the coronary circulation, which can only increase to a limited degree because of the existing coronary stenosis, can no longer keep up with the metabolic needs of the heart muscle. A test of this kind becomes necessary also in persons with diabetes, myxedema, or other types of hypercholesteremia, and in applicants for insurance or for positions of unusual responsibility or physical endurance, who may have no symptoms or dissimulate them.

Among the most common factors that can provoke coronary insufficiency are physical exercise, sympathetic stimulation, and epinephrine discharge caused by emotional factors or by cold. The epinephrine test in angina pectoris has been found too unreliable and dangerous,[5] since the individual response to injected epinephrine varies, and it is impossible to neutralize the effect of epinephrine rapidly.

The most easily controlled test is the electrocardiographic exercise test; this was first used in 1931 by Wood and associates,[6] who, however, did not recommend it for clinical use. The test first applied widely by Scherf and Goldhammer in 1932[7] consists of sitting up, doing knee bends, or climbing 1 to 3 flights of stairs, according to the severity of the patient's complaints; in this test, however, the amount of exercise cannot be controlled exactly, and an electrocardiogram cannot be taken at any time if serious symptoms should develop. These objections are eliminated in the "2-step test" designed by Master,[8-10] in which the patient walks up and down a short flight of stairs consisting of a central step 18 inches high and 2 side steps 9 inches high, while still attached to the electrocardiograph, so that a tracing can be registered immediately if angina pain should develop. The advantage of this test compared to the bicycle ergometer, leg exercise,[11] step-up tests,[12] or the treadmill[13] is that it requires minimum equipment and involves a type of work to which everyone is accustomed, thus minimizing the effect of training.

From the Cardiovascular Research Unit of the Division of Experimental Medicine, University of Vermont College of Medicine at the DeGoesbriand Memorial Hospital, Burlington, Vt.

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Another type of test (the hypoxia test) depends on a reduction of oxygen concentration in the inspired air (usually to 8 to 10 per cent) to provoke coronary insufficiency.[5] The advantages of this test over the exercise test are that it can be given to persons who are unable to climb stairs or follow instructions. Furthermore, since the electrocardiogram can be registered continuously, the test can be interrupted as soon as abnormalities appear even before pain develops; this can also be done, however, in the 2-step exercise test if special thoracic leads are used to register the electrocardiogram during as well as after exercise. Aside from the need for complicated and expensive special equipment, an important disadvantage of the test is that any normal person will develop anoxic changes in the electrocardiogram if the blood oxygen saturation becomes low enough. Because of the individual variations in pulmonary ventilation, dead space, and diffusion a given oxygen concentration in inspired air corresponds to a wide range of oxygen saturation in the blood. Accordingly, the test has been found less reliable in the diagnosis of coronary disease than the exercise test.[1-5, 14, 15] Furthermore, unpleasant or dangerous side-effects such as extreme dyspnea, cyanosis, pulmonary edema, headache, and even loss of consciousness with clonic cramps occasionally occur during the hypoxia test, but not during the exercise test. Accordingly, the hypoxia test should probably be carried out only when the exercise test is not feasible, and in patients whose circulatory reaction to anoxia or low barometric pressure is to be studied (e.g., skin divers, pilots, and patients traveling in only partially pressurized aircraft or about to be submitted to gas anesthesia).

The original Master 2-step test was developed as a test of "circulatory efficiency," and prescribed a specific number of ascents to be carried out in 1½ minutes for each sex, age, and weight; this number corresponded to the greatest number of ascents that permitted the systolic blood pressure and the heart rate to return to within 10 "points" of the resting value within 2 minutes after termination of exercise, as determined empirically on a large number of normal persons.[16] Ford and Hellerstein[17] found that the increase in oxygen consumption during and after the Master test is approximately the same in all persons regardless of sex, weight, and age, and amounts to about 7 times the resting value. This corresponds to an approximately 100 per cent increase in cardiac output.[18] Since the work of the heart during exercise is approximately parallel to the oxygen consumption,[19] the Master test can be expected to cause the same relative increase in cardiac work regardless of age, weight, and sex, and is therefore better suited to comparisons among different persons than a fixed amount of exercise. It corresponds to approximately the maximum work encountered in everyday life,[17] and is therefore not so strenuous as to endanger the patient or to cause the possibility of a physiologic coronary insufficiency, which has been seen in extreme exertion.[3, 5, 20]

The external work performed during the Master test for a given sex and weight (table 1) decreases with age about 20 per cent from the early twenties to the late sixties. This is probably due to the fact that physical activity and the degree of training decrease with advancing age. Training has been found to result in a decreased oxygen cost and heart rate response[19] for a given amount of external work. The lesser work prescribed in Master's table for children and teenagers than for adults, and for women than for men, is partly also due to a greater degree of training in adult men, but probably largely to the fact that a child or a woman of the same weight and age as a man is likely to be overweight. Since fatty tissue has a low metabolic rate, the resting oxygen consumption and cardiac output of such a person would be close to his original or normal weight, and the same amount of work would be expected to cause a greater increase of cardiac output, expressed as a percentage of the resting value, than in a tall, lean person of the same weight. This is also the reason why the external work in the table, expressed as a percentage of the body weight, decreases with increasing weight

Table 1

Standard Master Two-Step Test

Age:	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
Weight													
40-49	35	35	33										
50-59	33	35(33)	32(32)										
60-69	31	33(32)	31(30)										
70-79	28	32(30)	30(29)										
80-89	26	30(28)	29(28)	29(28)	29(28)	28(27)	27(26)	27(24)	26(23)	25(22)	25(21)	24(21)	23(20)
90-99	24	29(27)	28(26)	28(27)	28(28)	27(25)	27(24)	26(23)	25(22)	25(22)	24(21)	23(20)	22(19)
100-109	22	27(25)	27(15)	28(26)	28(26)	27(25)	26(24)	25(23)	25(22)	24(21)	23(20)	22(19)	22(18)
110-119	20	26(25)	26(23)	27(25)	27(25)	26(24)	25(23)	25(22)	24(21)	23(20)	23(19)	22(18)	21(18)
120-129	18	24(22)	25(22)	26(24)	27(24)	26(23)	25(22)	24(21)	23(20)	23(19)	22(19)	21(18)	20(17)
130-139	16	23(20)	24(20)	25(23)	26(23)	25(22)	24(21)	23(20)	23(19)	22(19)	21(18)	20(17)	20(16)
140-149		21(18)	23(19)	24(21)	25(22)	24(21)	24(20)	23(19)	22(19)	21(18)	20(17)	20(16)	19(16)
150-159		20(17)	22(17)	24(21)	25(20)	24(20)	23(19)	22(19)	21(18)	20(17)	20(16)	19(16)	18(15)
160-169		18(15)	21(16)	23(20)	24(19)	23(19)	22(18)	22(18)	21(17)	20(16)	19(16)	18(15)	18(14)
170-179		(13)	20(14)	22(19)	23(18)	23(18)	22(17)	21(17)	20(16)	19(16)	18(15)	18(14)	17(13)
180-189			19(13)	21(18)	23(17)	22(17)	21(17)	20(16)	19(16)	19(15)	18(14)	17(14)	16(13)
190-199			18(12)	20(17)	22(16)	21(16)	21(16)	20(15)	19(15)	18(14)	17(13)	16(13)	15(12)
200-209				19(16)	21(15)	21(15)	20(15)	19(14)	18(14)	17(13)	16(13)	16(12)	15(12)
210-219				18(15)	21(14)	20(14)	19(14)	18(13)	17(13)	17(13)	16(12)	15(11)	14(11)
220-229				17(14)	20(13)	20(13)	19(13)	18(13)	17(12)	16(12)	15(11)	14(11)	13(10)

Number of ascents in 1½ minutes (values for women are in parentheses). Age is expressed in years, weight in pounds. Condensed from Master et al.[3]

(this decrease is about 45 per cent between the weights of 85 and 225 pounds). In the original tables[16] Master used a correction for height but later dropped it for the sake of simplicity. It is possible that by introducing a similar correction the tables would correspond better to the individual case. A correction for the degree of training and for the emotional response of the patient would be highly desirable, but these factors do not lend themselves readily to quantitation.

When the duration of exercise in the Master 2-step test was doubled (that is, double the prescribed number of ascents was carried out in 3 minutes), the percentage of abnormal electrocardiographic responses in typical angina was considerably increased while the response in normal persons was not appreciably changed.[3] This is probably because with the rate of exercise prescribed in the Master test a steady state of oxygen consumption is not reached until 2 or 3 minutes after beginning the exercise, and even later in persons with beginning heart failure;[17, 18] extending the duration of exercise to 3 minutes therefore results in a more accurate and predictable increase of cardiac work. Master therefore recommends that if the single test is within normal limits, a double test should be repeated on the next day or at least 1 hour after the single test. In many laboratories this procedure is followed only in patients with borderline resting electrocardiograms, or severe anginal complaints, while the double test is given from the beginning in patients whose resting electrocardiogram is completely normal and whose anginal complaints are slight or absent.[14, 20] At any rate, the patient is instructed to stop exercise and lie down immediately as soon as he feels any distress, unusual fatigue, dyspnea, or his usual anginal pain; the test can also be interrupted by the operator as soon as serious electrocardiographic changes appear, if a thoracic electrocardiogram is registered during exercise. In some patients anginal complaints are precipitated by emotional upsets, meals, or exposure to cold more readily than by exercise alone. If the double Master exercise test does not produce pain or significant electrocardiographic changes in such patients, it would be of value to repeat the test under these conditions, e.g., while a piece of ice wrapped in gauze is held in each hand,[21, 22] or after a meal.[4, 23] If these methods do not produce significant electrocardiographic changes or symptoms, it may be necessary to repeat the double test on successive days, increasing the rate of exercise 10 per cent each day up to 30 per cent until either of these signs appears.

While exercise after a meal, after medication with atropine, or in hot or cold surroundings does not lead to definitely abnormal electrocardiographic changes in normal persons, the degree of the abnormality appearing in coronary disease may be influenced by these factors.[4, 5, 21–23] If the effect of certain therapeutic procedures is to be studied, it is therefore advisable to carry out the exercise test under as constant and as nearly basal conditions as possible; under these conditions and in patients showing definite electrocardiographic changes of coronary insufficiency after the Master exercise test, these changes can be reproduced quantitatively on the same or successive days.[24, 25] Over a period of several years, however, the response to the Master test was reproducible in only about 40 per cent of the patients.[26] If vasodilating drugs such as nitroglycerin, nitrites, or aminophylline are taken a short time before exercise, the usual electrocardiographic changes on exercise may not appear.[4, 5, 24–27] Therefore, such medication should be avoided on the day of the test. Digitalis may cause an apparently abnormal electrocardiographic response to exercise, even if the resting electrocardiogram shows no trace of digitalis effect.[5, 20, 28, 29] It is therefore necessary to withhold digitalis medication for at least 2 weeks before the test. The test should also not be carried out within 1 week of a cold, since abnormal electrocardiographic changes on exercise have been observed in normal persons during convalescence from infections.[4, 5, 30]

An exercise test should not be carried out if resting electrocardiogram shows definite

changes attributable to acute coronary insufficiency (i.e., true S-T segment displacement). It may be done in myocardial infarction more than 1 month old, when only QRS changes remain,[31] or in the presence of the pattern of left ventricular hypertrophy or of bundle-branch block with only secondary T and S-T changes,[32] or of borderline T and S-T changes[33] (e.g., low T waves and a horizontal S-T without depression). In all these cases it is necessary to make certain that the patient does not have the symptoms of impending myocardial infarction; if anginal complaints appear at rest or without apparent cause, the electrocardiogram should be repeated after a few days and the test should be done only if there is no change. The exercise test may precipitate or aggravate myocardial infarction once coronary thrombosis has started. Although more than 50,000 exercise tests have been reported in the literature, the occurrence of myocardial infarction on the day following the test was reported in only 6 instances, and in none of these were the above precautions observed;[34] in most cases the electrocardiogram had returned to normal following the test,[1, 34] so that the coincidence of the test and the myocardial infarction was probably fortuitous.

In the original Master test, the patient is asked to walk faster or slower, if it becomes apparent that he will not complete the required number of trips in 1½ or 3 minutes; this may cause a variable rate of exercise during the last trips of the test, by which the subsequent electrocardiogram is influenced most. This difficulty can be remedied partly by controlling the number of trips completed at the end of each 30-second interval of the test. Another solution is to have the patient climb each step to the rhythm of a metronome, allowing 2 counts for the ascent, 2 for the descent, and 1 for turning around; the number of counts per minute can be determined from table 1 by multiplying the number of ascents by 10 and dividing by 3.[20] In this case, it is well to have the patient practice walking in time to the metronome for 1 or 2 ascents before beginning the test proper.

A direct-writing electrocardiograph with an "instomatic" switch is essential for the exercise test. Since small displacements of the S-T segment must be evaluated, it is important to obtain clear definition of the baseline by proper positioning and temperature of the stylus; the rectangular styli give better definition than the V-shaped ones. The sensitivity should be adjusted accurately to 1 mv. per cm. Wandering of the baseline must be avoided by using an electrocardiograph with a built-in voltage stabilizer, vigorous application of electrode paste, and, if necessary, asking the patient to hold his breath during registration. The test should be carried out only in the presence of a physician well acquainted with electrocardiographic interpretation, and only after registration of a complete 12-lead resting electrocardiogram, which enables him to decide what type of test to give, if at all. The precordial electrodes are fastened in the V_4, V_5 and V_6 positions by means of a special rubber strap provided with most electrocardiographs; slipping during exercise can be prevented by fastening the strap at the back of the patient, carrying the loose end over the left shoulder, and fastening it again at the V_4 precordial electrode. To facilitate rapid switching among the precordial electrodes, the precordial lead cable can be provided with a spring clamp (battery clamp); during exercise this cable is left in the V_4 position, since this is usually the most "sensitive" lead. The leg electrodes are best fastened just above the calf, and the cables inserted from above. The arm electrodes are fastened on the wrist with the cable inserted from above or just below the shoulder with the cable inserted from below; the latter method causes a considerable reduction of muscle tremor. When the patient walks, he holds the crotch of the cable in his left hand and always turns toward the electrocardiograph after each descent of the 2-step stairs. If the patient keeps his right arm hanging loose at his side, it is possible to register CR_4 during exercise at 30-second intervals;[35] after exercise it can be switched to the V_4 position. Leads I and II as well as 3 precordial leads

are registered in rapid sequence, for 6 to 10 seconds each, immediately, and 2, 4, and 6 minutes after exercise. If the electrocardiogram has not returned to normal after this time it should be repeated also at 8 and 10 minutes.

Since exercise is always accompanied by hyperventilation, which may produce considerable T-wave changes even in normal persons,[36, 37] it is advisable to ask the patient to breathe as deeply and rapidly as he can for 30 seconds and to register the same electrocardiographic leads immediately before the exercise test.

The electrocardiographic changes most important in the diagnosis of coronary insufficiency are those of the T wave and S-T segment, and it is important to know the normal behavior of these electrocardiographic components during and after exercise.[5] The sympathetic stimulation that appears at this time leads to an increase in voltage of the P wave and of the atrial T wave (T_a or T_p wave) that follows it. This wave has a direction opposite to that of the main area of the P wave and a duration corresponding to that of the ventricular T wave. As long as the P-R interval remains within normal limits, the T_p wave is superimposed on the P-R interval, the QRS complex, and the initial portion of the S-T segment. Because of tachycardia the descending branch of the elevated U wave also becomes superimposed on these deflections. As a result, the P-R segment assumes a more or less steep downward course and causes the S-T junction to appear depressed when compared to the beginning of the P wave or to the beginning of the QRS complex.

Master considered that the normal depression of the S-T junction after his exercise test should not exceed 0.5 mm., measured from the level at the end of P-R in any lead, but such a depression was actually found in 6 to 25 per cent of apparently normal persons.[4, 12, 13, 17, 20, 24, 28, 38, 39, 41] It was therefore proposed[4, 5, 20] to measure the depression of the S-T junction not from the end of the P-R segment but from a straight line continuing the end of this segment into the QRS complex (fig. 1). The upper edge of a thin transparent ruler or of a piece of cellophane tape folded upon itself can be used as a straight line for this purpose. However, even when the "false S-T depression" caused by the T_p and U waves was eliminated in this way, 30 (12 per cent) of 243 apparently normal persons still showed S-T depression exceeding 0.5 mm. after the double Master exercise test.[20] On the other hand, if the normal limit of S-T depression is raised to 0.75, 1, or even 2 mm., the percentage of typical cases of angina pectoris showing such changes decreases from 60 to 98 per cent to 20 to 40 per cent and the percentage in apparently normal persons is still 2 to 5 per cent.[20, 24, 28, 38, 39, 41] The same is true if the duration of the electrocardiographic changes is taken to differentiate the normal from the abnormal response. None of our apparently normal persons had a true S-T depression of 2 mm. or more, lasting 4 or more minutes, but less than a third of patients with true angina showed such a response.[20]

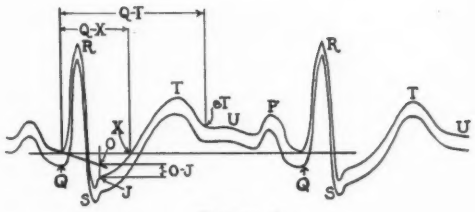

Figure 1

Methods of measurement of S-T segment depression. Point "O" is the point of intersection of a tangent to the terminal portion of the P-R segment with a vertical line passing through the S-T segment junction ("J"). True depression of the junction corresponds to the distance O-J. Point "X" is the point of intersection of the S-T segment with a line connecting the points of origin ("Q") of 2 consecutive QRS complexes. The horizontal distance Q-X is expressed as a percentage of the Q-T or Q-eT interval ("eT"= end of the T wave).

A possible means of differentiation between normal and abnormal S-T depression is that the normal S-T depression, which is caused by more rapid repolarization of the myocardial cell at rapid heart rates, would be expected to affect predominantly the portion of the S-T segment immediately following the

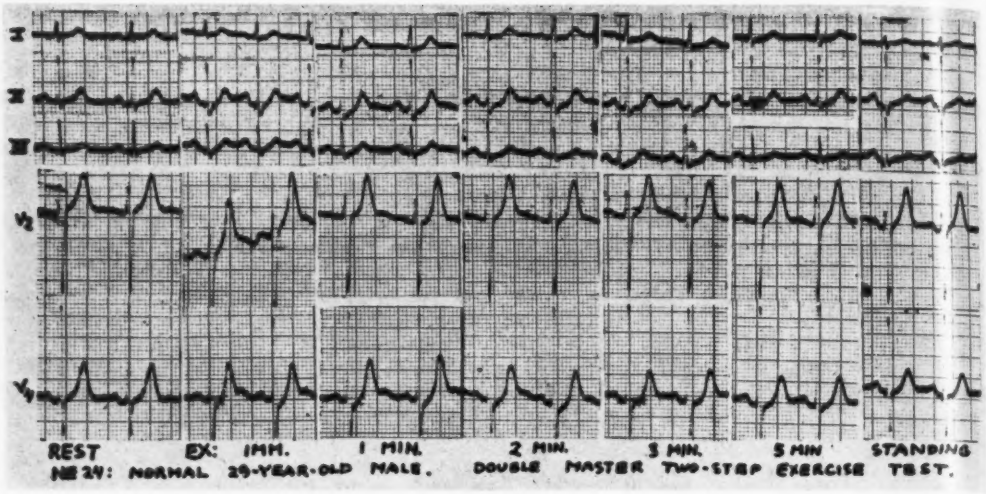

Figure 2

Electrocardiographic response to a double Master exercise test of a normal 29-year-old man, showing false S-T depression in leads II and III and true junctional S-T depression (Q-X not exceeding 40 per cent of Q-T) in lead V_4, immediately through 2 minutes after exercise.

QRS complex, or the S-T junction, leading to an ascending course of S-T[5] (fig. 2). On the other hand, S-T depression caused by coronary insufficiency is due to development of an injury current (incomplete repolarization or depolarization) in the subendocardial muscle layers of the left ventricle;[5] this injury current would be expected to persist throughout the entire systole, and therefore cause depression of the entire S-T segment. Robb, Marks, and Mattingly[14] have differentiated the normal, junctional, or ascending type of S-T depression from the "ischemic," horizontal, or descending type, which also involves the middle portion of the S-T segment or its entire length. Of 920 persons subjected to the double Master exercise test and followed up to 10 years, the death rate from coronary disease per 1,000 person-years of observation was 24.1 in persons showing the typical "ischemic" type, 6.9 in those showing a borderline "ischemic" type, 3.8 in those showing the "junctional" type, and 3.1 in those showing no depression or one less than 0.5 mm., in any one of the recorded leads.[14]

In order to quantitate the configuration of the depressed S-T segment, the author proposed[20] to express the duration of the interval between the beginning of QRS and the point where the depressed S-T segment crosses the baseline (point X in figure 1; Q-X interval) as a percentage of the duration from beginning of QRS to the end of the T wave (Q-T interval). This percentage would be much less dependent on the heart rate than the absolute duration of the depressed S-T segment. It was found that the best differentiation between apparently normal persons and those with typical angina was S-T depression of 0.75 mm. or more beyond the continuation of the P-R segment into QRS, with Q-X exceeding 50 per cent of Q-T, persisting for at least 2 minutes after exercise; still this behavior was found in 3.6 per cent of apparently normal persons.[20] It is possible that a higher degree of accuracy could be obtained if S-T displacement were expressed as a percentage of the QRS voltage in the same lead. Extracardiac factors such as the distance of the heart from the chest wall and the conductivity of the tissues surrounding the heart (e.g., emphysema or obesity) should influence the

voltage of QRS in the same way as that of S-T depression. This question will be the object of further study.

In his original studies Master considered inversion or isoelectric configuration of T in leads I, II, or V_4 as an abnormal response; later he stated "minor T waves changes alone are less significant but definite T wave inversion is probably abnormal."[9] Inversion of T in leads II, V_4, or V_6, without significant changes of S-T, after the exercise test was reported in about 1 per cent of nearly 1,500 tests in apparently normal persons,[20] but may appear in left ventricular hypertrophy. Acheson[12] found T-wave inversion without S-T changes after vigorous exercise in 2.3 per cent of 300 apparently normal men below the age of 40 and 1.7 per cent of 240 similar men above this age. He concluded that this type of T-wave inversion is probably independent of the development of coronary disease. In the combined series of Robb, Marks, and Mattingly,[14] followed up to 10 years, deaths from coronary disease were 3.6 per cent in the 110 persons showing only T-wave changes and 2.0 per cent in the 1,126 persons showing a normal response, as contrasted to 17 per cent in the 215 persons showing "ischemic" S-T depression.

T-wave inversion in normal persons may be due to two mechanisms. Persons with QRS complexes of high voltage and duration and low resting T waves (this is especially common in tall, slender persons) may show T-wave inversion in leads showing positive QRS area when the heart rate becomes fast, simply because of the normal decrease of the ventricular gradient with the heart rate. The ventricular gradient in such persons usually does not show a significant decrease when it is corrected for heart rate[26] (fig. 3). This gradient may allow differentiation between this normal variant and a borderline abnormal response. Injestion of potassium was seen to prevent this response in some cases.[42] The second type of T-wave inversion appears also in leads V_2 to V_4, where the main area of QRS is negative, usually when the heart rate has almost returned to resting values (fig. 4); it cannot be due, therefore, to decrease of the ventricular gradient. All persons showing this type of T-wave inversion were women; in some of them it also appeared after hyperventilation without exercise.[20] The mechanism of this type of T-wave inversion is not clear, but it can also be prevented in some cases by ingestion of potassium.[37] Perhaps the high incidence of women among persons showing this type of T-wave inversion is related to the longer persistence in women of the almost identical juvenile T-wave pattern, which can also be normalized by ingestion of potassium.[5]

In typical angina pectoris, T-wave inversion often follows significant S-T depression after the exercise test, and usually appears at a time when the heart rate has almost returned to normal values[5, 20] (fig. 5). It is probably caused by delayed repolarization in and around the regions of the left ventricle that showed the acute injury current immediately after exercise, possibly because of loss of potassium, calcium, or magnesium from the cell.[5] There are no statistical studies available, but the general impression is that persons who show significant changes of both S-T and T tend to have more severe angina than those with S-T changes alone. In asymptomatic persons after exercise this pattern was much more common in persons over 40 (1.7 per cent) than those under 40 (0.3 per cent); it is therefore more likely to be caused by early coronary disease.[12]

It has been suggested[20] that an excessive elevation of the T wave after exercise signifies a pathologic response. An elevated T wave of pointed configuration can be expected to appear as a late phase of the subendocardial injury pattern in leads that previously had shown depression of S-T, just as pointed, inverted T waves appear in subepicardial injury in leads showing S-T elevation.[5] On the other hand, elevation of T is also part of the physiologic response to exercise, where it can be caused partly by elevation of serum potassium, and partly by an increase of intraventricular temperature gradients due to increased cardiac heat production.[5] Elevation of T was present in over one half of all ap-

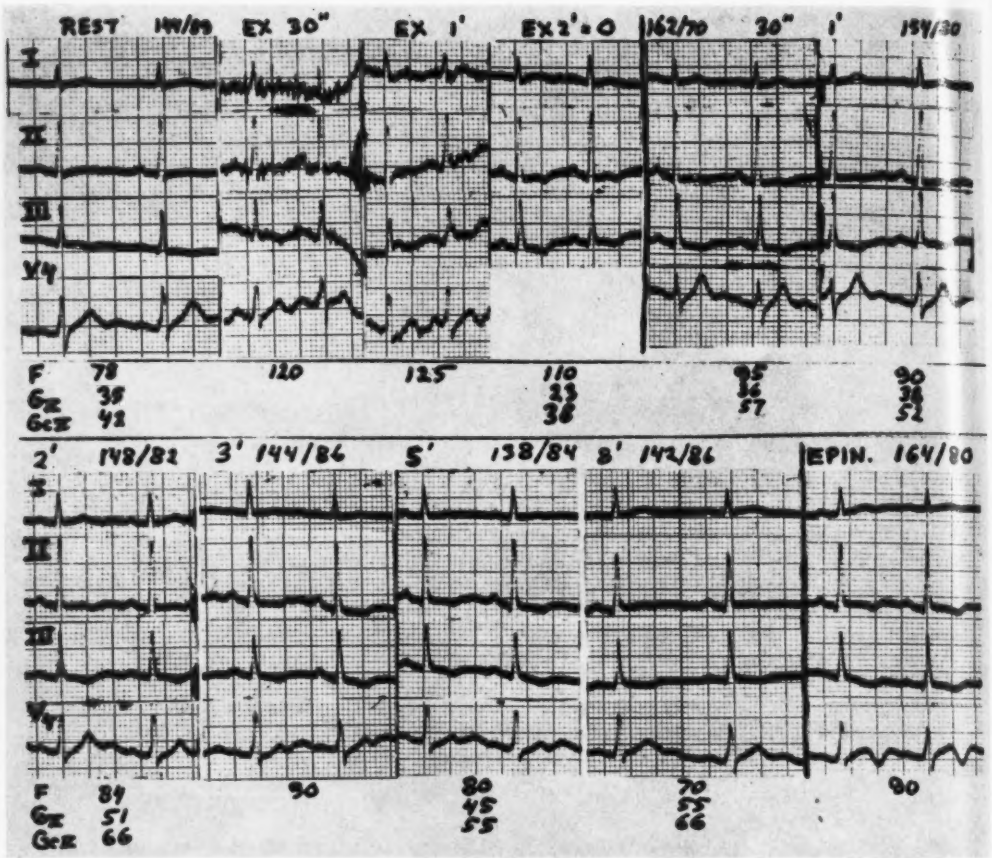

Figure 3

Electrocardiographic response of a normal 23-year-old man to leg exercise in the recumbent position for 2 minutes, at a rate of work corresponding to the Master test. Inversion of the T wave without significant S-T segment depression in leads II and III. The same changes could be reproduced by tachycardia due to injection of epinephrine ("epin"). F, heart rate; GII, ventricular gradient in lead II; GcII, same gradient corrected for the heart rate.[5]

parently normal persons, in whom it may reach 5 mm. or 3 times the resting value.[20] In typical angina pectoris elevation of T may exceed these values, but this happened in only 10 per cent of the cases.[20]

Abnormal changes of T and S-T after exercise in coronary disease are caused largely by differences in repolarization of the heart muscle cells in different regions in the heart.[5] If the entire ventricular muscle showed a repolarization delay, the form of the T wave would not be modified appreciably but the Q-T duration, corrected for the heart rate (Q-Tc) would be abnormally prolonged. In normal persons Q-Tc increases during exercise, as long as the heart rate is rising, since Q-T is slow to adapt to sudden changes of heart rate and remains relatively long. After exercise Q-Tc is shortened as long as the heart rate is slowing down, but returns to resting values 5 to 10 minutes after exercise.[5, 21, 43] In persons with coronary disease Q-Tc usually

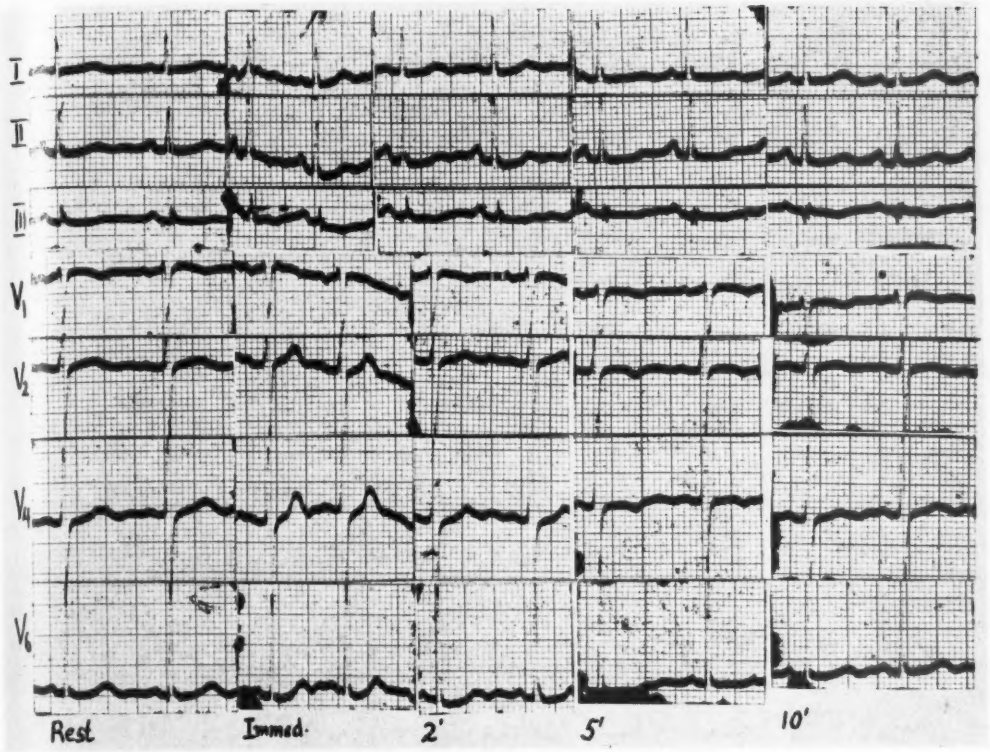

Figure 4

Electrocardiographic response to the double Master exercise test of an apparently normal 43-year-old woman, showing inversion of T in leads II and III and V_2 to V_4 with false S-T depression in lead II; true S-T depression in this lead is less than .05 mm.

shortens only slightly during exercise but becomes prolonged beyond resting values in the recovery phase, attaining maximal values 10 minutes after exercise; this prolongation is greater in patients showing an abnormal response of T and S-T.[5, 29, 43] A significant prolongation (more than 0.012 or about 3 per cent of the resting value) was found in a much higher percentage of patients with angina pectoris than significant changes of S-T and T.[29, 43] The prolongation of Q-Tc was absent in persons in whom abnormal S-T and T-wave changes appear after exercise as a result of digitalis medication, and this could be a convenient point of differentiation.[29] These findings have yet to be confirmed in a larger series. One important source of error would be that persons without coronary disease who show only a slight increase of heart rate during exercise or a secondary acceleration during recovery would also tend to show prolongation.

Inversion or diphasic form of the U wave has never been seen to appear after exercise in persons without symptoms of coronary stenosis; it appeared in about one third of the latter cases and was usually accompanied or preceded by significant S-T depression.[20] A few cases have been observed, however, in which U-wave inversion was the only abnormal sign after exercise.[20, 26] Care must be taken not to confuse a notched U wave extending to the following QRS complex with a diphasic U wave. Inversion of U in angina

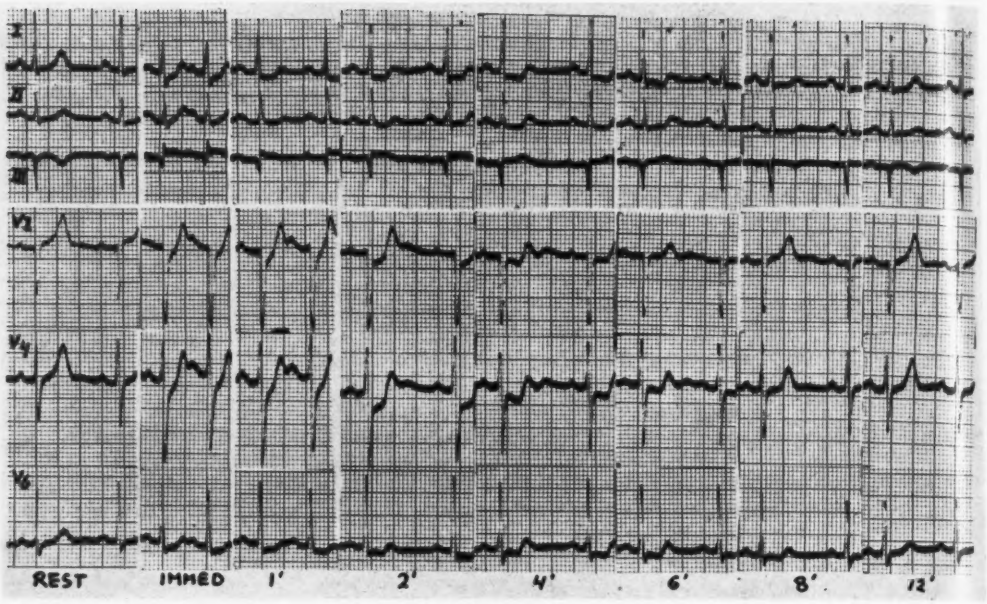

Figure 5

Significant depression of S-T and inversion of T in leads I and V_4 to V_6 after a single Master exercise test in a 76-year-old man who complained of occasional tightness in the epigastric region accompanied by an ache in the arms. These sensations were present at the end of the test, but disappeared after 3 minutes. The resting electrocardiogram is identical with one taken 2 days previously; it is still within normal limits but may represent an old posterior myocardial infarction scar. The Q wave and S-T elevation appearing in lead III after exercise would be in keeping with this interpretation.

may be related to altered dynamics of ischemic cardiac muscle, as demonstrated in the precordial pulse curve.[2]

In his original work, Master considered the appearance of conduction disturbances, bundle-branch block, or premature beats as part of an abnormal response to his test, but recently he concluded[38, 40] that they are of little diagnostic significance. Bundle-branch block is actually likely to appear whenever a critical heart rate is exceeded, regardless of the underlying cause.[5] Single premature beats (not more than 1 in 6 seconds) were as common (13 per cent) in apparently normal persons with questionable changes of T and S-T as in anginal patients with significant changes, but in normal persons without changes they were less common (3.5 per cent).[20] The increased ventricular distention caused by increased stroke volume and blood pressure during and after exercise may facilitate the appearance of ectopic beats regardless of their cause. Multifocal ventricular premature beats or short runs of ventricular tachycardia have been seen sometimes during exercise or during spontaneous attacks of angina pectoris[5, 20, 35] but not in normal persons; such changes should probably be regarded as indicating coronary stenosis. In many persons with premature beats after exercise but an otherwise normal electrocardiographic response the sensation of precordial pressure that they experienced after exercise was caused by the premature beats rather than by myocardial ischemia, as it disappeared when the ectopic beats were abolished by quinidine.[26]

A difficult question is the evaluation of the electrocardiographic response to exercise in

the presence of left ventricular hypertrophy. Half of the apparently normal asymptomatic persons who showed significant S-T depression in our group had mild hypertension,[20] and the percentage of persons with hypertensive or aortic valvular heart disease without anginal complaints who showed S-T depression exceeding 1 mm. after the Master test in other series varied from 13 to 90 per cent.[17, 30, 44] In the pattern of left ventricular hypertrophy with a high positive QRS area and low T waves in left precordial leads, any acceleration of the heart may cause T to become diphasic and S-T to become depressed due to a decrease of Q-T duration and the ventricular gradient.[5] To be sure, increase in diameter of muscle fibers alone makes diffusion of oxygen into the interior of the fiber more difficult and, together with the increase in myocardial oxygen consumption resulting from increased cardiac work, may lead to coronary insufficiency.[5, 17] In case of aortic valvular disease additional factors that may lead to coronary insufficiency are a low mean arterial pressure and the possibility of syphilitic coronary stenosis. In all published and personal cases of left ventricular hypertrophy without anginal complaints, however, the abnormal S-T and T-wave changes after exercise were confined to leads with a large positive QRS area and were usually accompanied by inversion or more negative configuration of the T wave, as in the typical pattern of left ventricular "strain."[26] If significant S-T depression appeared also in leads with negative mean area of QRS, or was accompanied by peaked and elevated upright T waves, typical symptoms of angina pectoris were usually present. This was also the case if the U wave became more inverted after exercise; in the pure ventricular "strain" pattern the U wave usually became more positive.[26]

We know that bundle-branch block in itself does not necessarily indicate heart disease,[5] and an exercise test can be of value in making the diagnosis of coronary stenosis also in this condition.[32] In right bundle-branch block the effect of tachycardia is to accentuate the slight elevation of S-T and tall T waves in leads with deep and wide S waves (lead I, II, and V_4 to V_6) and the depression of S-T and inversion of T in leads with wide R′ waves (usually leads II, III, and V_1 to V_2). A slight but significant S-T depression in leads I, II, and V_4 to V_6 may therefore be masked, but marked changes will appear in spite of block and are therefore all the more significant. This applies, in lesser degree, also to all leads showing deep S waves in persons without definite bundle-branch block. In left bundle-branch block, on the contrary, accentuation of the secondary changes of T and S-T due to tachycardia leads to the same type of abnormality as coronary insufficiency, and this can accordingly be suspected only if S-T depression occurs in leads with negative or only slightly positive net area of QRS, or if it is accompanied by a change of the T wave in a positive direction. The same considerations apply also in cases of the Wolff-Parkinson-White syndrome, in which the delta wave is upright in leads I, II, and V_4 to V_6.

In healed myocardial infarction, when only QRS or borderline T-wave changes remain, it may be of importance to determine how well healing has taken place and collateral circulation has developed, or how much coronary stenosis is present in other parts of the coronary arteries not affected by the occlusion that has led to the infarction. If even the double Master exercise test does not lead in significant displacement of S-T, the probability is that development of collateral circulation and the condition of the remaining coronary arteries are adequate for the average stresses occurring during daily life. In some cases the S-T displacement seen during the acute stage of the original infarction was seen to recur after exercise;[5] this can mean only that collateral circulation became inadequate. In other cases typical S-T depression as in angina pectoris without infarction appeared;[5, 31] this indicates that there is diffuse coronary stenosis in addition to the myocardial scar. Sometimes both types of S-T displacement occur at the same time in different leads (fig. 5).

Many cases have been reported in which

abnormal T waves and S-T segments in angina or old myocardial infarction have become more normal after exercise.[1, 5, 45] In 1 case this behavior was explained by a hypothetical secondary improvement of the coronary circulation caused by increased blood pressure or coronary dilatation due to liberation of vasodilator substances from the ischemic myocardium, since anginal complaints, which were present at the beginning, also disappeared toward the end of exercise ("second wind").[46] This latter feature seems to be characteristic of the "variant form of angina" described by Prinzmetal and co-workers,[10] which is attributed to spasm of a diseased coronary artery rather than organic stenosis. In the majority of the reported cases, however, the normalization was probably due to a secondary elevation of T and S-T caused by tachycardia in leads with a negative QRS area, to superposition of the normal elevation of T after exercise, or to the appearance of a beginning acute injury current in the region of an old myocardial infarction or localized coronary stenosis. In a small percentage of cases elevation of S-T as in acute myocardial infarction appears transiently after exercise or in the spontaneous attack of angina;[5] in these cases the typical Q waves of myocardial infarction usually develop soon in leads previously showing S-T elevation.[5, 10, 45] The S-T changes may be attributable in these cases to a severe stenosis of a smaller coronary artery branch rather than to a mild stenosis of a larger branch. When coronary stenosis is mild, most of the blood passing through it in systole is channeled into the more subepicardially situated arterioles, since intramyocardial systolic pressure decreases continuously from the subendocardial to the subepicardial muscle layers; this leads to greater myocardial ischemia in the subendocardial muscle layers, and the typical depression of S-T in unipolar leads facing the affected area.[5] On the other hand, when coronary stenosis is severe, both subendocardial and subepicardial muscle layers suffer from ischemia sufficient to cause an injury current, and the result is a systolic potential difference between the entire region of the ventricular wall supplied by the stenotic artery and the remaining parts of the ventricle; this difference causes S-T elevation in unipolar leads facing the affected area.[5]

A completely normal electrocardiographic response to the double Master exercise test indicates with great probability that no major coronary *stenosis* is present, or if it is present, it is well compensated by collateral circulation. This does not mean absence of coronary *sclerosis*. There is no complete certainty that a given patient may not develop a lethal acute coronary thrombosis with myocardial infarction a few hours after a normal exercise test; from a statistical point of view, however, his life expectancy is 8 times greater than if he had a definitely abnormal response. One theoretical possibility of a normal response in spite of major coronary stenosis is that the affected artery is so small that the muscle region supplied by it is completely surrounded by normal muscle; the injury currents at the boundary of this region could then completely neutralize each other. Another possibility is that the degree of coronary stenosis is intermediate between one leading to predominantly subendocardial and one leading to transmural localization, and that injury currents on the boundary between subendocardial and subepicardial muscle are partly neutralized by those between the latter and the normal muscle. A further possibility is that injury currents set up by 2 transmural lesions on opposite sides of the ventricle or by a subendocardial lesion and a neighboring transmural lesion may partly cancel each other. Such cancellation, however, cannot be expected to be complete. If a sufficient number of leads is recorded at small enough intervals after exercise, one of the localizations is bound to outweigh the other in some of these leads or at some time during development of ischemia and recovery from it.

If the electrocardiogram remains normal after the double Master test and anginal complaints of the patient do not appear, the conclusion that no major coronary stenosis is present at the time is still justified. There is

still the possibility, however, that a functional stenosis may be precipitated by factors that are not present during the exercise test. If the correct diagnosis is important enough to justify the additional time and effort, the test can be repeated under conditions that are found to precipitate the complaints, or the rate of exercise can be gradually increased. If the electrocardiogram and subjective feelings are closely observed also during exercise, there is little danger of permanent damage to the myocardium. Also, if the double Master test is normal, there is reasonable probability that the coronary circulation would be adequate also in moderate hypoxia, but the hypoxia test should probably be made if a conclusion with a high degree of certainty is needed.

When criteria of the configuration and duration as well as the magnitude of S-T depression are used, a definitely abnormal response to exercise (e.g., true "ischemic" type S-T depression of 1 mm. or more) indicates coronary insufficiency with a high degree of probability. If, however, the electrocardiographic changes are less definite, involve only the T wave, or if marked tachycardia, ventricular hypertrophy, or pulmonary disease are present, the changes must be evaluated with great caution. The apparently abnormal responses reported in persons with neurocirculatory asthenia[5] would probably no longer be considered abnormal with the new, stricter criteria. Appearance of similar changes after hyperventilation without exercise is strong presumptive evidence for their functional nature. It has been stated that if the response to the exercise test becomes normal after medication with certain ergot drugs, the response is purely functional, but many observations have been reported of the same response in persons with typical angina.[5] Recently, it has been observed that an abnormal response due to coronary stenosis may become normal if the test is repeated with inhalation of oxygen, but functional abnormalities are not usually influenced;[42] on the other hand, functional changes are more likely to become normal after ingestion of potassium than the former.[42]

In this review the expression "positive" or "negative test" has been purposely avoided. Just as the degree of coronary stenosis and the many other factors that may aggravate or counteract its effects show a continuous gradation in different persons, so does the degree of electrocardiographic abnormalities. No test, and certainly not the exercise test, can be expected to furnish black and white information concerning the presence or absence of coronary disease. At any rate, the conclusions gained from the electrocardiographic exercise test must be based on careful consideration of the electrocardiographic and clinical peculiarities of each individual case, and even then they can be versed only in terms of probability, never of certainty. The electrocardiogram is still only an adjunct in the clinical diagnosis of angina pectoris, although its importance has increased considerably during the last 20 years.

Summario in Interlingua

Le diagnose de stenosis coronari es facile a facer super le base del anamnese sol in casos in que typic symptomas de angina de pectore es presente. Tamen, quando tal symptomas es absente, le diagnose deveni plus difficile.

Es discutite le valor del electrocardiogramma post exercitio pro le diagnose de morbo cardiac coronari. Le conclusion es que iste test non differe de alteres in le facto que illo es incapace de fornir precise decisiones nigro-blanc concernente le presentia o le absentia de morbo coronari. Le conclusiones derivate ab le electrocardiogramma post exercitio debe prender in consideration omne le particularitates electrocardiographic e clinic del caso individual, e mesmo alora tal conclusiones pote esser presentate solmente como probabilitates e nunquam como certitudes. Le electrocardiogramma es non ancora plus que un adjuncto in le diagnose clinic de angina de pectore, ben que il es ver que su importantia ha crescite considerabilemente in le curso del passate 20 annos.

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This is not the place for an extended discussion of the curriculum and the teaching methods and similar problems of medical education. But I would point out again that since there is too much factual knowledge and practical skill to impart in so short a period of time as four years, the part of wisdom seems to me to lie in training the student's capacities rather than stuffing his memory. What capacities? The capacity to observe, to reason, to compare his observations and reasoning with those of others, and the capacity to put himself in his patient's place—compassion. With such abilities trained, sharpened, and refined, the graduate of a medical school would find in his fifth, or intern year, and later as assistant resident and resident, the opportunities to use and refine those capacities to the immediate and the infinite advantage of his patients and himself.—Alan Gregg, M.D. *Challenges to Contemporary Medicine.* New York, Columbia University Press, 1956, p. 112.

CLINICAL PROGRESS

The Clinical Pattern in Certain Types of Occlusive Cerebrovascular Disease

By CLARK H. MILLIKAN, M.D., ROBERT G. SIEKERT, M.D., AND JACK P. WHISNANT, M.D.

ONE of the principal purposes in delineating clinical patterns that are as complex as the various categories of occlusive cerebrovascular disease is to enable the physician to distinguish one type from another, in order to institute the most efficacious treatment. Our presentation will deal with diagnosis.

It is now our practice to divide the cerebral arterial circulation into 2 systems: the carotid and the vertebral-basilar. There are practical reasons for this division as well as an interest in accuracy of diagnosis for accuracy's sake. These reasons include (1) a probable higher incidence of warning episodes before a major stroke in the vertebral-basilar system, (2) a much higher mortality rate in basilar than in carotid thrombosis (about 60 per cent in basilar and 15 per cent in carotid), and (3) a higher incidence of atherosclerotic lesions in the carotid system that are accessible, in the neck, to extracranial surgical therapy. The last-mentioned reason ultimately may or not prove to be important.

Figure 1 illustrates some but not all of the predominant sites of atherosclerosis in the larger arteries of the extracranial and the intracranial cerebral circulation. Emphasis is placed on the segmental nature of the lesions. This does not always occur, however, since in certain instances the pathologic change can extend over several centimeters.

Only in the past decade has attention been directed to the existence of the stenosing lesions shown in the extracranial portions of the internal carotid, vertebral, common carotid, and innominate arteries. The exact significance of these lesions is not known, and much careful clinical work will be required to establish whether or not they are frequently or only seldom related causally to focal cerebrovascular insufficiency and infarction. It is true that patients often have these lesions without ever having any clinical evidence of cerebrovascular disease, and in rarer instances occlusion of a carotid or even a basilar artery has not been associated with abnormal symptoms or signs. It is likely that many patients having these lesions will be treated surgically unnecessarily (endarterectomy) before the significance of the lesions is accurately assessed. While few patients will have stenosis at all sites shown in figure 1, involvement at more than one site is common.

In clinical work different methods that include pathologic, physiologic-pathologic, and clinical-physiologic-pathologic studies have been adopted for classifying cerebrovascular disorders. Recently we have found a temporal clinical classification an extremely useful procedure in relation to both diagnosis and treatment. By means of such a classification the clinician attempts to define the existing activity of the pathologic physiology evident in a precise history and on examination. The categories are as follows: (1)

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

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Table 1

Three Clinical Categories for Strokes

Incipient or impending stroke: Neurologic examination generally gives normal results; some warning signs indicate that the patient is likely to have a stroke.
Advancing stroke: Active progression of neurologic deficit during period of observation (hours).
Completed stroke: Stable neurologic deficit of variable degree followed by improvement over days or months.

incipient or impending stroke, (2) advancing stroke, and (3) completed stroke (table 1).

Impending or Incipient Stroke

Impending or incipient stroke indicates that at some future date the patient is likely to or probably will have a serious stroke with permanent residuals (table 1). As yet, our ability to make such a prognosis is far from precise and much needs to be learned about the two types of intermittent focal cerebrovascular insufficiency that make up this category, that is, intermittent insufficiency of the carotid system and intermittent insufficiency of the vertebral-basilar system.

These designations are clinical ones and are presumed to be produced by decreased blood flow in one of the major cerebral arterial systems. Both syndromes are characterized by attacks made up of one or more neurologic phenomena that depend on the region of brain where the blood supply is insufficient. Such attacks come on quickly and often progress to maximal degree in a few seconds. Each attack can last for an hour or more but the duration commonly is 5 to 20 minutes. Abatement of the attack will be almost as swift as the onset and the patient will be left in a normal state. If a patient has many attacks or a few severe attacks, a minor or slight neurologic deficit may result. It is thought that cells may be damaged permanently if subjected to repeated severe bouts of hypoxia, each one of which is sublethal. In this way a neurologic deficit of mild degree could "accumulate" during a series of attacks of intermittent insufficiency. For an individual patient there is generally marked similarity between attacks, with some variation more commonly noted in bouts of vertebral-basilar insufficiency than in those of carotid insufficiency.

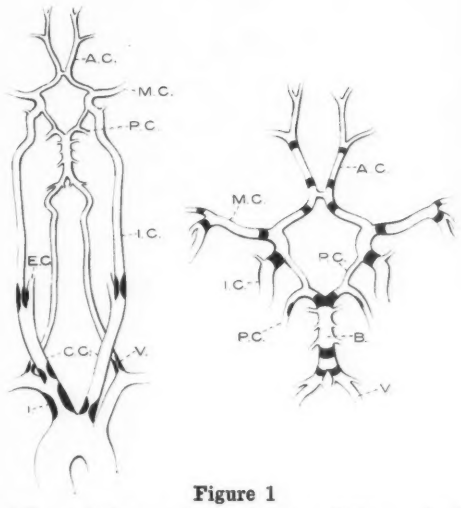


Figure 1

A.C., anterior cerebral; M.C., middle cerebral; P.C., posterior cerebral or posterior communicating; I.C., internal carotid; E.C., external carotid; C.C., common carotid; V., vertebral; I., innominate; and B., basilar.

Intermittent Insufficiency of Vertebral-Basilar System

The symptoms often recounted in an attack of vertebral-basilar insufficiency are listed in table 2. Seldom will a patient have all of these. Rather there will be a pattern of several symptoms such as weakness of a hand and arm, or dizziness and slurring of speech. Because of overlap between carotid and vertebral-basilar symptoms there may be difficulty in a few instances in correctly identifying the system involved. Certain symptoms occur much more frequently during attacks of vertebral-basilar insufficiency. These include blindness, dimness, or cloudiness throughout all portions of the visual fields, double vision, severe dysarthria, dysphagia, and most frequent of all, vertigo often with nausea and vomiting. There may be a changing pattern of weakness or paralysis. If involvement moves from one side of the body to the other

Table 2

Intermittent Insufficiency of Vertebral-Basilar System

Episodes, sudden in onset and generally of 5 to 20 minutes' duration, characterized by the following combinations:
Monoparesis, hemiparesis, or paralysis occasionally shifting from side to side and potentially involving all or any combination of extremities.
Sensory defects commonly affecting both sides of the body
Bilateral defects throughout visual fields
Diplopia
Vertigo
Dysarthria
Dysphagia
Alteration of consciousness

Table 3

Intermittent Insufficiency of Carotid System

History:
Transient episodes of:
Weakness or numbness limited to one side of the body
Aphasia if dominant hemisphere is involved
Impaired vision in eye on side of lesion
Physical signs in some instances:
Diminished pulsation in carotid artery on involved side
Relative hypotension in retinal artery on involved side (ophthalmodynometer)
Bruit over carotid artery or eye on the involved side

in different attacks, or if both sides of the body are involved in a single episode, the ischemic region is almost certainly receiving a supply of blood through the vertebral-basilar system.

In general, the diagnosis cannot be made with reasonable certainty unless two or more of the symptoms (table 2) are present during an episode. A possible exception to this statement consists of attacks of loss or severe impairment of vision throughout all visual fields of both eyes. This is referred to as bilateral homonymous hemianopsia and is almost pathognomonic of the disorder. Episodic vertigo is an extraordinarily common complaint. It does not appear wise to make a clinical diagnosis of vertebral-basilar insufficiency unless the symptom, vertigo, is definitely linked with one or more of those listed (table 2). Between attacks of vertebral-basilar insufficiency, abnormal neurologic or other physical signs do not betray the presence of vertebral arterial disease.

Intermittent Insufficiency of Carotid System

Table 3 lists the symptoms often recounted in an attack of carotid insufficiency. At the time of an individual attack all or only a portion of these may be present. Weakness is the most common. If the insufficiency is of the carotid to the dominant hemisphere, aphasia in global or fragmentary form is usual. This is infrequent in vertebral-basilar insufficiency and can aid in correct identification of the origin of the attack. Even more definitely localizing is unilateral impairment of vision in the attack, which not only indicates insufficiency of the carotid system but also points to the portion of the system proximal to the take-off of the ophthalmic artery as the likely locus of atherosclerotic stenosis. Diplopia, bilateral homonymous hemianopsia, dysphagia, vertigo, and bilateral impairment of motor or sensory function are not included as symptoms. Only in cases of multiple stenosis, occlusion of one vessel and stenosis of another, or abnormal anatomic relationships, are these symptoms part of the clinical picture of intermittent carotid insufficiency.

There are three possible important abnormalities that may be detected on examination of a patient having intermittent insufficiency of the carotid system. Pulsation of the suspected artery may be decreased or absent. Since variation of pulsation may be normal, such a sign is of questionable value. A bruit over the appropriate vessel is more important evidence of stenosis. Ordinarily such a sound can be distinguished from a transmitted cardiac sound and may indicate stenosis of the artery at the point of maximal intensity of the bruit. A bruit over the ipsilateral or contralateral eye is of lesser significance. Finally, a relative decrease of pressure in the retinal artery on one side is substantial evidence of stenosis in the parent system. An absolute relationship does not exist between brachial

blood pressure and retinal blood pressure. Therefore, it is mandatory to test the pressure in both eyes. A difference of 12 to 15 mm. of mercury between the two eyes is significant but not absolute evidence of stenosis or occlusion.

The physician must remember that attacks that consist of a focal neurologic deficit may result from some other type of brain lesion such as a benign, malignant, or metastatic neoplasm, an abscess, and scarring secondary to injury. In rare instances tumors can exactly mimic intermittent focal cerebrovascular insufficiency. If the patient (1) does not have any clonic or other convulsive motor activity, (2) does not have a change of consciousness, (3) is well between attacks, and (4) has a normal or near normal electroencephalogram, a mistake in diagnosis is rare indeed. In most cases the diagnosis is reasonably clear from the history alone. The physician seldom needs to rely on arteriography, pneumoencephalography, or ventriculography for differentiation. Meniere's disease, migraine, and syncope cause little difficulty in diagnosis to the physician who takes a detailed history.

The site of the stenotic or occluding lesion in the system cannot be determined from the symptom pattern unless a bruit is detected, the pressure in the retinal artery is significantly low on one side, or vision on one side is impaired. In vertebral-basilar insufficiency the occurrence of bilateral homonymous hemianopsia appears more likely with atherosclerosis in the basilar as contrasted to the proximal segments of the vertebral arteries, but this does not seem to be a one-to-one relationship. When a carotid bruit signals stenosis at the origin of the internal carotid artery as the source of attacks, there is no assurance that a second or third lesion may not be present distal to the detected one. This knowledge is of paramount importance in assessing a patient for cerebral arterial surgery and in ultimately judging results. Thus, in certain instances a carotid stenosis may be suspected of producing attacks of insufficiency while the responsible lesion is in the middle cerebral artery!

Table 4

Mechanisms of Attacks of Insufficiency

Atherosclerosis plus:
Transient hypotension
Polycythemia
External compression or kinking
Anemia
Multiple emboli
Smoking
Vasospasm
Beginning thrombosis

Mechanisms of Attacks of Insufficiency

Table 4 lists a number of mechanisms that might produce intermittent focal cerebrovascular insufficiency. Discussion of each item is not the purpose of this paper but rather to emphasize that at present it is presumed that the primary or static defect is atherosclerosis. For instance, without stenosis, transitory hypotension will produce simple syncope, but with stenosis, a transitory focal neurologic change results. Smoking and multiple emboli are included because of known association with these syndromes rather than because of conviction concerning their importance. It is important that the physician screen each patient for causes of transitory hypotension, external compression of vessels by unusual compression of the artery when the head is turned, polycythemia, and anemia. Correction of any such discovery may relieve the attacks.

Advancing Stroke

The second major clinical category is the progressing or advancing stroke. In this group ischemia is of such duration and severity that relatively permanent to very severe damage is produced. Such a stage may begin exactly like an attack of carotid or vertebral-basilar insufficiency; instead of abating in a few minutes, however, it generally worsens, often in steps, until the neurologic deficit may be severe and extensive when significant infarction has taken place. At such a time the clinician must postulate that (1) stenosis, probably due to advancing thrombosis, is increasing, (2) collateral supply has failed to provide the blood needed, or (3) prolonged

Table 5

Thrombosis in Carotid System

History: Antecedent warning episodes.
Symptoms indicating a focal lesion in one hemisphere, progressing over hours
Neurologic deficit: Monoparesis to hemiplegia
Hemianesthesia
Homonymous visual-field defect or impaired vision in eye on side of lesion
Aphasia (dominant hemisphere)

Table 6

Thrombosis in Vertebral-Basilar System

1. Antecedent transient episodes (75 per cent)
2. Neurologic syndrome developing during hours or a few days with progression frequently in stuttering or stepwise fashion
3. Neurologic deficit including combinations of
a. Bilateral visual-field defects
b. Nystagums
c. Impaired ocular rotations, particularly internuclear ophthalmoplegia
d. All or any combination of limbs exhibiting an upper motor neuron type of weakness
e. Sensory changes, also variable in distribution
f. Dysarthria
g. Dysphagia
h. Impairment of consciousness

decreased supply produces defective function in more and more brain cells.

During an attack, it is not usually possible to determine the moment at which the clinical state, called "focal intermittent insufficiency," will change into an irreversible process. However, if a patient who has had a dozen attacks of 10 minutes' duration each of left hemiparesis and impaired vision of the right eye is seen after an hour or 2 hours of *paralysis* of the left side of the body, great genius is not required to detect that this event is different from the usual attack. If another hour of observation reveals new phenomena such as a left Babinski reflex and beginning of a sensory defect, it is amply clear that the problem is one of an advancing stroke and that it is no longer an attack of relatively harmless carotid intermittent insufficiency. If infarction due to thrombosis is causing the progressing stroke, worsening may continue, by steps, for a good many hours. In contrast, an infarct secondary to embolism attains full, or almost full, pathophysiologic development in seconds to a few minutes. Progressing strokes due to thrombosis are divided into those in the carotid system and those in the vertebral-basilar system. Diagnostic criteria that apply to both types are as follows: (1) history of antecedent or warning attacks of intermittent insufficiency, (2) steplike progression over many minutes or hours, (3) rather minimal amount of pain in the head, particularly when in the carotid system, (4) preservation of consciousness generally, and (5) clear cerebrospinal fluid. Often other evidence of atherosclerosis in heart, kidneys, or extremities is present.

Thrombosis in the Carotid System

In addition to the general diagnostic points, thrombosis in each system is commonly attended by certain anatomically determined neurologic symptoms and signs. These are listed for the carotid system in table 5. It is recalled that in carotid intermittent insufficiency, certain physical signs referable to the patency of the appropriate carotid system might be suggestive. Exactly the same thing may be true in progressing thrombosis in the carotid system. For instance, measurement of both retinal artery pressures may assist greatly in the diagnosis.

Thrombosis in the Vertebral-Basilar System

Table 6 lists phenomena often observed in progressing thrombosis in the vertebral-basilar system. Certain combinations of impairment of bilateral visual fields, nystagmus, dysphagia, and weakness of bilateral extremities with altered reflexes are relatively characteristic, when correlated with the history, of vertebral-basilar thrombosis. Only observation can detect whether or not the stroke is in a progressing stage. As in intermittent insufficiency in this same system, the combination or pattern of the signs in a given patient permits diagnosis.

In addition to combinations of the signs listed in table 6 there are special arterial clinical syndromes within the vertebral-basilar

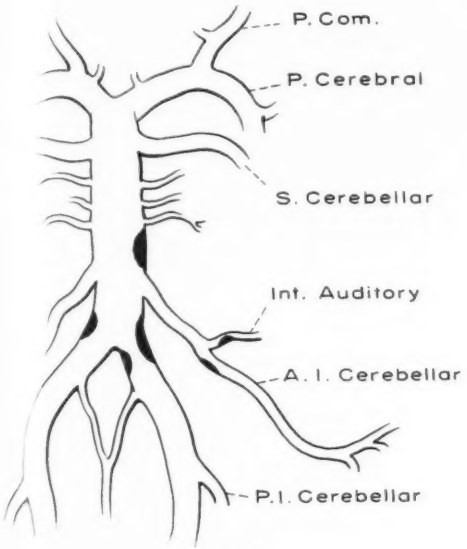


Figure 2

Branches of the so-called parent system of the vertebral-basilar system.

system, two of which will be mentioned. Figure 2 shows some of the branches of the parent system. One of these is called the "internal auditory system." This vessel leaves the intracranial cavity through the internal auditory meatus and traverses the internal auditory canal, ultimately dividing to supply the cochlea (hearing) and the labyrinth. If the entire artery is occluded the patient will complain of sudden loss of hearing in that ear and will experience severe nausea and vomiting. Audiograms reveal total loss of hearing, and caloric tests show absence of response indicating a dead labyrinth on the same side as the loss of hearing. The loss of hearing is generally permanent. Vertigo is extreme but the patient gradually improves, so that in 6 weeks to 3 months he is fairly comfortable. If there is occlusion of the arterial branch to the labyrinth only, the patient has a very sudden (in seconds or minutes) onset of severe vertigo with nausea and vomiting. Hearing is not disturbed. Nystagmus will be present during the first days or weeks of the illness and caloric tests will show that one labyrinth does not function. Symptomatic recovery ensues in 6 weeks to 3 months. Occlusion of the arterial branch to the cochlea causes sudden unilateral complete loss of hearing, usually permanent, but no dizziness or demonstrable defect in labyrinthine function.

Table 7

Lateral Medullary Syndrome (Occlusion of Posterior Inferior Cerebellar Artery)

Vertigo, nausea, vomiting
Dysarthria
Dysphagia
Ipsilateral palatal palsy
Ipsilateral Horner's syndrome
Ipsilateral involvement of pain and thermal sensation on face
Contralateral involvement of pain and thermal sensations on limbs and trunk
Ipsilateral ataxia of limbs

Lateral Medullary Syndrome

The second special-vessel syndrome to be mentioned is that caused by an infarct in the superior-lateral portion of the medulla, often due to occlusion of the posterior inferior cerebellar artery. The general phenomena are those observed in progressing cerebral thrombosis. The special components of the syndrome are listed in table 7.

These two special-vessel subdivisions of progressing stroke are included because of characteristic clinical pictures and because they point out additional, more important differences. Occlusion of the internal auditory artery is a "one shot" stroke and is not characterized by long progression or recurrence. Occlusion of the posterior inferior cerebellar artery also is generally without recurrence. It is likely that little can be done in the way of treatment at the time of onset and that therapy to prevent recurrence is not needed in most instances. Occasionally the thrombus causing the infarct will propagate and produce additional symptoms; this then becomes a stroke in evolution. These examples of nonlethal subcategories in a highly lethal category (vertebral-basilar thrombosis) indicate how complex the diagnosis and treatment of cerebrovascular disease are becoming.

Table 8

Embolic Arterial Occlusion: Criteria for Diagnosis

1. Sudden development of signs of a local brain lesion (within seconds or a few minutes)
2. Absence of prodromal manifestations in most cases
3. Relative preservation of consciousness
4. Existence of a source of emboli usually in the heart (either cardiac arrhythmia or infarction)
5. Evidence of recent embolism in: Other organs, that is, spleen, kidney, extremities, intestines, or lungs Several regions of the brain in different cerebrovascular territories

Table 9

Intracerebral Hemorrhage: Criteria for Diagnosis

1. Grossly bloody cerebrospinal fluid
2. Hypertension
3. Rapid evolution of hemiplegia and other phenomena over minutes or hours
4. Onset generally during activity
5. Headache (if patient is sufficiently conscious to report his symptoms)

Embolic Arterial Occlusion

Another type of stroke is that caused by embolism. Table 8 lists important phenomena in the diagnosis of cerebral embolism. The onset and development of maximal neurologic deficit is so swift that the physician rarely will see this syndrome progress. The characteristic onset in a few seconds or minutes, absence of discomfort and absence of a history of antecedent warning attacks, demonstration of a source of emboli, and previous embolic phenomena in other organs make up the typical complex of symptoms and signs. The heart is the commonest source of emboli. Atrial fibrillation, other arrhythmias, mitral disease, subacute bacterial endocarditis, and myocardial infarction are diseases that can lead to the formation of emboli.

Myocardial infarction, which is relatively silent, should be considered when embolism seems clinically possible. If any question exists, one or more electrocardiograms should be obtained to clarify the problem. Currently there is inconclusive evidence that any primarily effective treatment exists for cerebral embolism. Precise differential diagnosis, however, may make possible the early treatment of cerebral thrombosis or may assist in preventing future emboli to the brain and other organs.

Intracerebral Hemorrhage

The category of progressing strokes should include hypertensive intracerebral hemorrhage. Intracranial surgical therapy is of value in a few instances but if the physician is considering anticoagulant therapy or extracranial vascular operation, an accurate diagnosis is mandatory. Table 9 includes symptoms and signs of clinical value in the diagnosis of intracerebral hemorrhage. Gross blood in the cerebrospinal fluid is at the top of the list. If one can exclude traumatic spinal puncture, blood in the cerebrospinal fluid establishes a basic diagnosis of intracranial hemorrhage. If the clinician is uncertain about the diagnosis of the type of stroke, the cerebrospinal fluid should be examined. Only a small amount of fluid need escape. Seventy-five to 85 per cent of all patients having intracerebral hemorrhage will have gross bleeding into the fluid. The development of neurologic phenomena generally occurs within minutes to hours, and is smooth, that is, without the steplike progress so common to infarction.

Pain in the head is often more severe and the outcome is more frequently fatal with intracerebral hemorrhage than with infarction. While bleeding into the brain can coincide with normal blood pressure, it often is associated with severe hypertension with the systolic pressure well above 220 mm. Hg and the diastolic more than 120 mm. Hg. History reveals absence of warning attacks and that the stroke has started during activity rather than rest. Both these factors are important; the first is often present in cerebral infarction, which commonly occurs during sleep or rest. Prudent use of these items, interwoven with the positive and negative diagnostic criteria for cerebral thrombosis and embolism, leads to accurate clinical diagnosis in the majority of instances.

Acute Subarachnoid Hemorrhage

Such hemorrhage generally due to the rupture of an intracranial aneurysm must be considered in the differential diagnosis of a progressing stroke. Table 10 includes the clinical phenomena produced by this condition. Almost all patients have sudden onset of severe headache as the first symptom. This strikes in a second or two, is often in the occipital nuchal region at first, and may be likened to a heavy blow with a hammer. The headache is so severe from onset that the sufferer must stop whatever he is doing. Soon after onset of headache, nausea and vomiting are likely to develop. Examination reveals stiff neck on flexion and there may be rather typical preretinal hemorrhages noted by ophthalmoscopic examination. There must be grossly bloody cerebrospinal fluid at spinal puncture. Since there may be the appearance of a focal neurologic deficit to mimic some of those observed with cerebral infarction, the history and the spinal fluid examination are of paramount importance in differential diagnosis. Attention to these items makes diagnosis of acute subarachnoid hemorrhage possible in almost all cases.

Table 10

Subarachnoid Hemorrhage: Criteria for Diagnosis

1. Sudden onset of severe headache
2. Stiff neck on forward bending
3. Grossly bloody cerebrospinal fluid
4. An often relatively transitory disturbance of consciousness
5. Subhyaloid (preretinal) hemorrhages

Completed Stroke

The third major category is the completed stroke. A completed stroke means that the thrombosis or hemorrhage is no longer extending anatomic confines and that infarction or other damage has reached maximal involvement for the stroke. The clinical syndrome, whatever its nature, no longer progresses; it remains static for a few hours or improvement begins. Exactly the same principles of diagnosis for the subcategories apply here as already discussed. The problem in this group is to decide accurately in each case when the stroke is complete. The clinician must rely on simple observation and assessment. Particularly in thrombosis in the vertebral-basilar system, in which progression is commonly in stages or steps, an accurate statement concerning "completion" is a matter of relativity since there may be no progression for a number of hours and even for a day or two. In thrombosis in the carotid system, lack of progression for a few hours generally indicates that a stroke is complete, that is, there will be no worsening of weakness, sensory defect, aphasia, or other abnormality. After cessation of progression there may be a number of hours when the patient's condition changes little and then, unless damage has been extraordinarily severe, improvement begins. This phase of modest improvement is particularly characteristic of infarcts produced by thrombosis. It is less conspicuous with intracerebral hemorrhage. The early and continuing improvement so common in cerebral thrombosis may be of importance in establishing the diagnosis, particularly when there has been some reason to suspect the presence of a brain tumor or abscess. Because of the swiftness of onset and the absence of steplike progression, determination of the completion phase of cerebral embolism is relatively easy.

Arteriography in Strokes

What is the role of arteriography in strokes? The physician who obtains a precise history from the patient concerning every phase of the illness, performs a general examination and a neurologic examination, listens for bruits over the carotid arteries in the neck, measures the blood pressure in both eyes, and assesses a few pertinent laboratory tests can correctly diagnose a stroke and the type of stroke in more than 90 per cent of instances without arteriography. In the remaining difficult diagnostic problems, arteriography is generally indicated and may actually establish the correct diagnosis. In certain instances it has been possible to re-establish normal blood flow in an occluded or stenosed artery

by surgical intervention. Arteriography is the best known means of accurately determining the position and the degree of narrowing of the artery.

Of the 3 categories of stroke discussed, the first, that of impending stroke, appears to be the one for which arteriography provides the most useful information. In the second category, that of advancing stroke, there is grave question concerning the danger of and the length of time required for arteriography as well as the efficacy of surgical treatment. In completed serious strokes little purpose is served by arteriography. Aside from preparation for operation, arteriography is used as a research procedure for studying certain facets of strokes in medical centers.

Summary

This has been a summary of the clinical patterns in certain types of cerebrovascular disease with emphasis on occlusive disease. Knowledge concerning these categories is important in studying the results of various therapeutic technics and in selecting the correct treatment for some subdivisions where effective therapy exists.

Summario in Interlingua

Iste articulo summarisa le configurationes clinic de certe typos de morbo cerebrovascular, con attention particular prestate a morbo occlusive. Le cognoscentia de iste categorias es importante in studiar le resultatos de varie technicas therapeutic e in seliger le correcte tractamento in certe subdivisiones in que un efficace therapia es disponibile.

On Cardiac Murmurs

By AUSTIN FLINT, M.D.

By the limitations of the significance of the murmurs, I mean the actual amount of knowledge respecting valvular lesions to be derived from this source. It is evident, from what has been stated already, that the knowledge which they convey is of every great importance, but, important as this knowledge is, it has certain limits which are not always sufficiently understood; and, as a consequence, the practitioner is liable to fall into unfortunate errors of opinion as regards the gravity of the lesions which the murmurs represent.—*Am. J. M. Sc.* n.s. **44**: 29, 1862.

BOOK REVIEWS

Cardiac Auscultation. Including Audio-Visual Principles. Second Revised and Enlarged Edition. *J. Scott Butterworth, Maurice R. Chassin, Robert McGrath, and Edmund H. Reppert.* New York and London, Grune & Stratton, 1960, 102 pages 68, figures. $6.25.

The warm reception received by the first edition and the important advances in audiovisual technics in the intervening past 5 years have led to the appearance of the second edition. The text has been thoroughly revised and new illustrations have been liberally incorporated embodying stethograms and timing by reference to electrocardiograms and carotid pulse tracings. Advances in surgery have placed great responsibility for accurate diagnosis on the medical profession. Few would dispute the authors' assertion that the accuracy of diagnosis can be greatly enhanced by auscultation.

It is a tribute to the authors that in the 100 pages they encompass succinctly the historical aspects, the underlying physical principles, the methods of recording, and the diagnostic characteristics of heart sounds and murmurs in health and disease. Among the matters discussed are the inherent characteristics of the stethoscope that favor acuity of auscultation, the origin of the heart sounds and their components, as well as the physiologic and pathologic variations that are encountered. Throughout, the authors relate the auscultatory phenomena to hemodynamic events. The salient features of congenital and acquired heart disease are set forth clearly and concisely. The format and illustrations are superb, matters of considerable importance in a text on this subject. The book is heartily recommended to all physicians and particularly to students of cardiovascular disease.

HERRMAN L. BLUMGART, M.D.

Acute Pericarditis. *David H. Spodick.* New York, Grune & Stratton, Inc. 1959, 182 pages, illustrated. $6.50.

The author of this 182-page monograph has been interested in pericarditis for some time and has contributed to our knowledge of tuberculous pericarditis, cardiac tamponade, and the pain mechanisms of pericardial disease. In this day of the "population bomb" of medical papers, it is useful to have at hand a convenient summary such as this volume compressing our present information on a specific subject. Acute pericarditis lends itself well to such a review and to the digesting of the 361 papers in the bibliography.

There are 27 chapters that contain descriptions of anatomy, physiology, electrocardiogram, pain mechanisms, signs, symptoms, x-ray findings and other diagnostic data, etiology, complications, sequelae, and treatment. It would be difficult to find any cause of acute pericarditis not mentioned by the author, including the "pericarditis of uncertain origin," since some 50 etiologic agents are discussed. There are 28 well-chosen illustrations, a list of eponyms, and an index. This is an admirable little book to pull off the shelf for a ready reference.

The author does well to quote Jeremiah 17:9 "The heart is deceitful above all things and exceeding weak—Who can know it?" His book will help to answer that question.

HOWARD B. SPRAGUE, M.D.

The Plasma Proteins. Clinical Significance. *Paul G. Weil.* Philadelphia, J. B. Lippincott Company, 1959, 133 pages, 2 figures. $3.50.

This monograph is one of the "Practitioner Pocket Books" series and first appeared in the *American Practitioner and Digest of Treatment* in 1958. Following a chapter on the principles of the technics of protein fractionation is a review of the origins, properties, and functions of the plasma proteins. Rather than a comprehensive review of the changes in the plasma proteins in health and disease, the alterations in certain diseases are given to illustrate important points in protein metabolism. The therapeutic value of protein fractions and the significance of protein changes in various diagnostic tests are emphasized. The bibliography contains 49 references selected because they are review articles or represent fundamental contributions to the subject. The references are not incorporated into the text. This is a readable review of the current knowledge of the clinical importance of plasma proteins. It has limited value as a reference book.

HOWARD M. RAWNSLEY, M.D.

Your Heart: A Handbook for Laymen. *H. M. Marvin.* Garden City, N. Y., Doubleday and Company, 1960, 335 pages. $4.50.

In the author's words, "This book was written in the hope that it might bring clear understanding

of the heart's function and disorder to nonmedical readers." It accomplishes this purpose admirably, and will be of interest to physicians because of the simple formulations and explanations of symptoms that should allay anxiety in patients because of their fear of the unknown. The exposition is clear, lucid, and dignified, and the style is characterized by elegance without ever becoming ornate.

The initial chapters are concerned with a description of the heart and blood vessels, the arrhythmias, and then proceed to deal successively with rheumatic heart disease, high blood pressure, congestive heart failure, angina pectoris, and coronary atherosclerosis. In dealing with anticoagulant therapy, the heart in pregnancy, the importance of obesity, and the effect of tobacco smoking upon the heart, the author not only presents a résumé of our existing knowledge, but addresses himself also to the questions frequently raised by patients.

The A, B, C's of medical terminology are made available in a comprehensive glossary, which proceeds from Adams through Ballistocardiogram and Carcinoid syndrome to Xanthomatosis.

Throughout the book the author presents different points of view in regard to controversial questions in a most judicious and skilful manner. This book can be recommended with enthusiasm as a catechism for the intelligent layman and will also be found to be of interest to internists.

HERRMAN L. BLUMGART, M.D.

Biosynthesis of Terpenes and Sterols. Ciba Foundation Symposium. Edited by *G. E. W. Wolstenholme, and C. M. O'Connor.* Boston, Little, Brown & Co., 1959, 311 pages, 192 illustrations. $8.75.

The isolation of mevalonic acid—an acetate replacing factor which is an active precursor in the biosynthesis of squalene and cholesterol—was reported in 1956. Many important findings in the study of the biosynthesis of terpenes and sterols followed this most significant event. These and associated matters are the basis for the 17 reports presented in May 1958 at this Symposium which was attended by leading investigators from many countries. The papers and the discussion following each report are detailed and technical. Those interested in these important biochemical studies will find this symposium a valuable and absorbing survey of this subject.

PHILIP TROEN, M.D.

Introduzione alla Elettrocardiofia Vettoriale *L. Pozzi.* Edizioni Mediche Italiane, Firenze, 1960, 223 pages, 148 figures of which 5 are in color.

In the preface to this book Professor P. Rijlant, well-known Belgian physiologist, mentions that Dr. Pozzi is in charge of the electrocardiographic service of the oldest and largest hospital in Florence, and that in his endeavor to write an introduction to the basic electrical and physiologic principles underlying electrocardiography and its vectorial concepts he could use the council of prominent members of the Faculty of the University of Florence in question of physics, electrochemistry, physiology, and histology. Dr. Pozzi has also done some excellent experimental work on intraventricular conduction to which reference is made in the present book. The first one third of the book discusses basic principles of electricity, especially as applied to volume conductors, the second third describes the electro-chemical basis of myocardial action potentials, the spread of excitation in ventricular muscle and the conductivity of the heart and tissues surrounding it, while the third applies these principles to electrocardiographic leads. The most recent advances are considered throughout, and the figures illustrating them are abundant and well-chosen. The fundamental approach as well as the emphasis on the newest practical and theoretical concepts makes the book very useful for anyone who wishes to be able to interpret electrocardiograms intelligently.

E. LEPESCHKIN, M.D.

Arterial Embolism in the Limbs. *A. L. Jacobs.* Baltimore, William & Wilkins Co., 1959, 200 pages, 37 figures. $8.00.

This monograph reviews the clinical and pathologic experience with 122 episodes of peripheral arterial embolism in 69 patients studied by the author from 1938 to 1954. Detailed information is provided on the natural history, etiology, signs, symptoms, diagnosis, and pathology of the emboli. The discussion of variations in collateral circulation and the propagation of thrombi in relation to emboli is based on arteriograms and gross dissections of the involved extremities. Evidence is presented to indicate that neither propagating thrombi nor arterial spasm plays an important role in aggravating ischemia. The author states that limb survival rates following embolic occlusion are the same whether treated medically, surgically, or not treated at all. However, it is concluded that the probable fate of the ischemic limb can usually be decided 2 hours after embolization and that embolectomy is the treatment of choice when the larger limb arteries are obstructed.

STANFORD WESSLER, M.D.

Chirurgie der Arterien. *K. Kremer.* Stuttgart, Georg Thieme, Verlag, 1959, 259 pages. $14.50.

To write a concise and up-to-date textbook on arterial surgery in this day of rapid advances in this field admittedly is a difficult if not impossible

task. In spite of the inherent difficulties involved, Dr. Kremer has undertaken this task enthusiastically and with a scholarly approach. His text encompasses the entire field of arterial surgery, from an interesting chapter of history, through sections on operative technics, and materials used and processing of various types of grafts, to the latest developments in arterial bypass operations. In keeping with the title of the book, congenital abnormalities of the great vessels, as well as the surgical aspects of disturbed pulmonary and coronary circulation, are considered. Although he has included all aspects of arterial surgery within the space of 259 pages, the author has succeeded in bringing forth a concise text which should be particularly helpful to medical students and young physicians in postgraduate training. The book is written in clear modern German, which should be readily understood by American readers familiar with scientific German.

It would be surprising indeed if a task such as this were to be carried to completion faultlessly on the first attempt. The author most likely was anxious that the text be available as soon as possible for the wide circle of German students who needed it. Possibly as a consequence of this, traces of haste are detectable in the last chapters, whereas the first part of the book has great order and clarity.

Since a large body of scientific knowledge is covered in this work, it comes as no surprise to find that opinions expressed at times will be at variance with those of some readers. [In the experience of the reviewers, for instance, the Branham-Nicoladoni sign has seldom been encountered in the presence of congenital arteriovenous fistula, in which condition Kremer lists this as a diagnostic clue (p. 179).] Similarly, the recommendation that arteriography be performed immediately after an acute arterial occlusion (p. 185) probably will not be accepted generally. The author later acknowledges the possibility that this procedure might induce or further aggravate arterial spasm and further compromise the circulation.

The scholarly approach of the author already has been mentioned, and indeed, throughout the book as well as in the extensive and excellent bibliography appended to each chapter, there is ample evidence of painstaking scrutiny of the pertinent literature. Some readers will not share the view, expressed in several places, about the value of oscillography in the clinical evaluation of the patient. Perhaps slight overemphasis is applied to the mortality rate associated with aortic embolism (p. 189). In the section on disturbances of the coronary circulation it would have been better to omit the cursory discussion of the complex manifestations of coronary arterial disease and to refer the reader to texts on clinical cardiology.

On page 226 the claim is made that arteriography will distinguish between arteriosclerosis and thromboangiitis obliterans. Yet, when the reader examines the arteriogram (No. 138) showing a supposedly typical lesion of thromboangiitis obliterans, he finds that it shows segmental superficial femoral arterial occlusion, a type of lesion rarely seen in this disease.

The statement that both atherosclerosis and thromboangiitis obliterans are caused by a nutritional disturbance (p. 225) is an oversimplification, and could well have been avoided in a text such as this. When changes in the ocular fundi are ascribed either to atherosclerosis or to thromboangiitis obliterans, the pertinent question of whether hypertension is absent or present is left unanswered (p. 230).

In the chapter on surgical procedures on the sympathetic system, a concise statement as to the indications would have been welcome. Although it is presented as a historical reference only, the mention of cordotomy as a procedure for arterial hypertension or intractable ischemic pain (p. 233) will only confuse the uninitiated.

The reviewers have approached several points in this book in the spirit of critical analysis because they regard the work as an outstanding contribution, and one which undoubtedly will become one of the standard German texts in the field. For this reason the author is entitled to suggestions which may prove helpful in the preparation of forthcoming editions. Of the many outstanding features of the book, one which warrants emphasis is the author's over-all cautious approach to the question of arterial surgery and another is his critical questioning of long-term results based on the recognition that our present therapeutic measures do little to alter the basic process of occlusive arterial disease.

Thieme's publishing house has provided the book with the traditionally good print, excellent reproductions, attractive format, and handsome cover for which this publisher is noted. These features, in company with the outstanding text, will make it a volume of distinct value on the bookshelves of all students of vascular disease.

ALEXANDER SCHIRGER, M.D.
EDGAR A. HINES, JR., M.D.

Fortschritte der Kardiologie. Edited by *R. Hegglin and E. Lüthy.* Basel, S. Karger, 1959, 337 pages, 139 figures. sFr. 59.

Selected lectures from the Third World Congress of Cardiology held in Brussels in 1958 are presented under 4 major headings. The section on "Congenital and Acquired Heart Disease" includes

6 papers of surgical interest that though obviously dated with respect to details of operative technic, present excellent summaries by Bailey on the physiology of the mitral and aortic valves.

The sections on "Cardiac Failure," "Diseases of the Coronary Arteries," and "Correlations between Lung and Heart" contain a number of excellent summaries with fairly extensive bibliographies of basic biochemical and physiologic studies of congestive heart failure, coronary artery disease, and of the pulmonary circulation in disease states. Only in the longest of the book divisions, which cover hemodynamic and metabolic aspects of congestive heart failure, is there a systematic survey of the subject by the articles chosen.

Approximately one third of the text is in French with short English summaries which, however, are somewhat awkward. The remainder is well written in English.

The book is interesting and well worth reading. It suffers in that knowledge of the subject material is accruing so rapidly that keeping a book of this sort timely is difficult.

ANTHONY M. IMPARATO, M.D.

Diseases of Medical Progress. *Robert H. Moser.* Springfield, Ill., Charles C Thomas, Publisher, 1959, 131 pages. $4.75.

With this engaging title the slim volume by Dr. Moser graphically and succinctly runs the gamut of the misfortunes that may and do befall patients as a result of our therapeutic enthusiasms. The text is a "survey of diseases and syndromes unintentionally induced as the result of properly indicated, widely-accepted therapeutic procedures." As the author poignantly reminds us in his introduction, "The wise admonition of the ancients, 'At least do no harm,' acquires a new dimension when used in the context of modern medicine." The reviewer agrees with F. Dennette Adams who declares in the foreword that in so thoroughly surveying the literature and crystallizing the reported hazards of the many newer agents at our disposal, the author has rendered an important service to the medical profession and to the public.

In the 54 pages of the text, the author briefly alludes to hundreds of conditions produced by therapeutic measures. The chapter on disorders due to antibiotic-induced diseases includes septicemia, endocarditis, pseudo-membranous enterocolitis, staphylococcal diarrhea and pneumonia, tracheobronchitis, vitamin K and B complex deficiencies, neurologic disturbances, nephrotoxic effects, and penicillin reactions.

The second chapter dealing with cardiac diseases includes induction of arrhythmias by digitalis, electrolyte imbalances, quinidine, procaine amide, rauwolfia, and by many other drugs. The aggravation or precipitation of angina pectoris by hydralazine and ganglion-blocking agents is described. The hemorrhagic diathesis subsequent to anticoagulant therapy that leads to hemopericardium, tamponade, lesions in the skin, subcutaneous tissue, and rarely to bilateral adrenal hemorrhage is portrayed. The myocarditis following emetine, Fuadin, tartar emetic, and vaccination is mentioned. The collagen and collagen-like diseases are cited occurring after hydralazine, steroids, and other drugs.

Other chapters deal with iatrogenic hematologic disease, hepatic and gastrointestinal diseases, hormone-induced diseases, metabolic diseases including retrolental fibroplasia, low sodium syndromes, secondary gout, and renal diseases. The description of the manifold effects of long-term steroid therapy is of particular interest.

The book is admirably documented by 707 references so that details of each complication of therapy may be studied. The value of this book is heightened by an excellent index. Knowledge of these side effects and complications is essential to wise employment of the multitude of powerful therapeutic tools now fortunately placed at our disposal. This treatise is warmly recommended to all physicians as a valuable compendium for ready reference.

HERRMAN L. BLUMGART, M.D.

Metal Binding in Medicine. Proceedings of a Symposium Sponsored by Hahneman Medical College and Hospital, Philadelphia. Edited by *Marvin J. Seven,* and *L. Audrey Johnson,* Philadelphia, J. B. Lippincott Company, 1960, 400 pp., illustrated. $13.75.

This volume is an extremely well edited collection of formal presentations and panel discussions at a meeting held in Philadelphia in May 1959. The symposium is comprehensive in scope in that it includes many aspects of trace metal research as well as metal binding in the broad sense of a linkage between a binding agent and a metal. This term is distinguished from the narrower term "chelation," which is reserved for the process of metal binding in which the metal is incorporated into a ring structure. There are some sixty contributors and these have been wisely chosen in terms of their experience and authority in their respective fields. The material is divided into 6 groupings, each containing 5 to 9 chapters. Almost every phase of metal metabolism, distribution, and toxicology is considered. There are discussions of the pharmacology, toxicity, and therapeutic effects of chelating agents as well as the use of chelates in differential diagnosis, contrast roentgenography and the relationship to the action of drugs.

There are several negative features. The title is somewhat misleading if by the term medicine it implies that the book should be of considerable use to the physician in the practice of clinical medicine. The same criticism applies to many of the chapter titles in which the term clinical is used but the contents have little or nothing to do with clinical aspects. These titles often promise much more than is warranted by the limited knowledge in the field and the material actually presented. Most of the chapters merely represent an abstract of a paper previously presented by the author with detailed accounts of methodology and results, rather than an informative, critical, and objective review. This is often disappointing because it is difficult to read and sometimes of relatively little value to the clinical physician who is not engaged in the specific field of research. From the point of view of the reader of this journal who has a specific interest in diseases of the circulation, the chapters on metal binding in relation to normal cardiac function and arrhythmias and the use of chelates in the treatment of cardiac arrhythmias and coronary disease are most relevant and those which deal most with clinical aspects. However, these are among the less commendable in the volume because of excessive speculation and unconvincing experimental evidence. Most of the summaries are extremely poor in that they tell little more than is indicated by the title and provide little information to the reader who does not wish to examine the chapter verbatim.

Although these shortcomings detract from the value of the book for the clinical physician it nevertheless is a notable contribution and should prove of great value as a reference work to those who are especially interested in this advancing field of metal binding.

CHARLES F. FRIEDBERG, M.D.

On the History of Medicine. *Henry E. Sigerist.* Edited and with an introduction by Félix Martí-Ibañez. Foreword by John F. Fulton. M D Publications, Inc., New York, 1960, 313 pages. $6.75.

This volume could be reviewed most adequately by one who has long had a deep interest in medical history and who is familiar with other books in this field intended for the general reader. The present reviewer must acknowledge that he does not have these qualifications; his knowledge of medical history could be contained easily in the proverbial mustard seed. But possibly there may be some justification for the deliberate selection of a reviewer who must judge the book solely on its merits, without a background of historical knowledge, inasmuch as it does not require such knowledge for full understanding and enjoyment. Clearly the book was not intended to be limited to the small audience composed of those whose major interest has been the history of medicine.

There is a foreword by the late Dr. John F. Fulton, who made significant contributions to this special field throughout his adult life. For many years he and Dr. Sigerist were warm friends. There is also a luminous introduction, fittingly entitled "The Mind of a Man," by Dr. Félix Martí-Ibañez, Professor of Medical History at the New York Medical College. This is an eloquent, perceptive, enlightening, and deeply moving tribute to Sigerist by one who knew him intimately and who served as the editor of this volume.

The twenty-seven chapters of the book are divided into four classifications: On Medical History; Ancient and Medieval Medicine; Renaissance, Baroque, and Age of Enlightenment Medicine; Personal History. Ten of the chapters were lectures or talks given before medical or non-medical groups; several were formal addresses on special occasions.

Let it be said at once that I have read every chapter in the book at least once, and some of them several times. There are very few pages, if any, that cannot be read with full understanding by interested non-medical people; almost never does the author assume that his readers have previous knowledge of this branch of history. Inasmuch as his chapters cover a wide range of subjects, it is probable that most readers will find some of them more enlightening and entertaining than others. All are written with great clarity and with obvious mastery of the field of knowledge to which Sigerist devoted his life. In many there is quiet humor underlying the dignity, as in that entitled: "An Elizabethan Poet's Contribution to Public Health: Sir John Harington and the Water Closet." This entertaining account closes with the words: "It is most appropriate that our children colloquially call this convenience 'the john' since it was a John who gave it to us in its improved form—Sir John Harington."

Since I have already acknowledged that my past interest in medical history has been something less than overwhelming, it is perhaps understandable that the section entitled Personal History seemed to me the most fascinating and rewarding. This begins with a masterly valedictory address upon Sigerist's departure from Johns Hopkins University, where he had spent fifteen productive years as the immediate successor of the great Dr. William H. Welch. The chapter, entitled "Medical History in the United States: Past—Present—Future," is a stirring account that could have been written only by a thoughtful, experienced, wise, and deeply learned person. His address in Johannesburg upon receiving an honorary degree from the University of the Witwatersrand gives a fascinating and detailed account of his education

and the teachers who influenced him most: Arnold Lang, Friedrich von Muller, Ferdinand Sauerbruch, and Karl Sudhoff. His transfer to Baltimore from Leipzig, where he had succeeded Sudhoff as head of the Institute of the History of Medicine, is told very simply: "The Johns Hopkins Institute (of the History of Medicine) was opened in 1929. Sudhoff went to America for the occasion. Two years later, in 1931, I was invited as visiting lecturer. I spent two months at the Institute, whereupon I went on a long lecture tour through all sections of the United States. And while I was travelling I was offered Dr. Welch's chair."

The most personal, most intimate, chapter is that called "Living Under The Shadow." Here he says with apparent calmness: "The years have gone by, and now at the age of sixty I find myself with three incurable diseases." Two of these were not serious or threatening, but the third was hypertension. He makes it clear that this produced cardiac symptoms which limited his physical activities, but his comments upon these limitations reveal wisdom, patience, acceptance, and gratitude for the many preceding years of hard and rewarding work. The chapter closes with this sentence: "But whatever fate may have in store for us, we must be prepared to accept it and to die as we have lived, rejoicing at the thought that it was given to us to live through a fascinating period of history and to take an active and creative part in it on the progressive side to which the future belongs; rejoicing also in the knowledge that we are leaving children and former students behind who will carry on from where we stop." He died on March 17, 1957, at the age of 65 years, having completed only two of his projected eight-volume history of medicine.

To all who have even a faint interest in learning more about the special field in which Dr. Sigerist labored so joyously and effectively this volume is commended without hesitation.

H. M. Marvin, M.D.

Cinefluorography. Proceedings of the First Annual Symposium on Cinefluorography, Sponsored by the Department of Radiology, University of Rochester, School of Medicine and Dentistry, Rochester, New York, Friday and Saturday, November 14 and 15, 1958. Edited by *George H. S. Ramsey, James S. Watson, Jr., Theodore A Tristan, Sidney Weinberg,* and *William S. Cornwell.* Springfield, Ill., Charles C Thomas, Publisher, 1959, 292 pages, 143 figures. $11.75.

This book is largely a discussion of the technic of cinefluorography rather than a description of the clinical applications of the method. The editors have collected 18 papers presented at the symposium in 1958. Questions and answers in the discussion at the end of the papers are included and form a useful supplement. The first chapter introduces basic methods that have been employed in cinefluorography. Subsequent chapters describe in detail image-amplifier equipment that is available commercially or is in the development phase. Other papers discuss the problems of radiation dose, photographic lenses, recording cameras, relative merits of 16 mm. and 35 mm. photography, properties of films, methods of development and projection of film. There is a section on diagnostic analysis of cinefluorograms. Chapters on solid-state amplifying screens and fiber optics present interesting new material that may have practical applications. Finally a useful bibliography of about 300 papers is included. The illustrations are well reproduced. The book fills the purpose for which it was intended and should be read by those interested in this new and rapidly expanding field.

William L. Proudfit, M.D.

Diseases of the Chest, Including the Heart. Edited by *J. Arthur Myers.* Springfield, Ill. Charles C Thomas, Publisher, 1959, 1015 pages, illustrated. $34.50.

This compendium of over 1,000 pages is divided into 2 parts and consists of 48 chapters written by 34 authors. The 24 chapters of Part I deal with Diseases of the Chest including disorders of the lungs, pleura, diaphragm, and esophagus. The subjects discussed include the segmental anatomy of the lungs, symptoms of chest diseases, the evaluation of pulmonary function in clinical practice, pulmonary abscess, atelectasis, emphysema, tumors of the chest, and chest injury. The subjects of chapters on infections include the common cold, pneumonia, tuberculosis, pertussis, sarcoidosis, and the mycoses.

The last 400 pages of the volume consist of a survey of disease of the cardiovascular system. The opening chapter is a discourse on physical examination of the heart and great vessels, followed by a chapter on roentgenology of the heart, and on the principles of electrocardiography.

Practically every subject within the domain of the title of the book is at least mentioned, and 51 pages are devoted to the details of cardiac surgery. Each chapter is followed by ample bibliographic references for further study. The book is profusely illustrated by superb plates and figures.

The treatment of some of the subjects in a book of such wide scope as this cannot be sufficiently detailed to qualify as a reference source for definitive and detailed descriptions. Nor is it a volume to be used as a text. It is recommended, however, as a worthwhile additional reference source for medical libraries.

Herrman L. Blumgart, M.D.

Semeiologia Fonocardiografica. *G. Gigli* and *C. Muiesan.* Rome, Il Pensiero Scientifico Ed., 1959, 3[illegible] pages, 269 illustrations.

This monograph on phonocardiography by Gigli and Muiesan amalgamates features of those authored by Mannheimer, Calo, Caniggio, Butterworth, Schmidt-Voigt, Holldack, Weber, McKusick, and others. Its organization follows a logical progression from the general to the specific: physical and physiologic considerations in cardiovascular sounds, technical considerations in the recording of heart sounds, the general description of normal and abnormal heart sounds and murmurs, acquired heart disease, congenital heart disease, arrhythmias. The text is illustrated by 269 figures, most of them oscillographic phonocardiograms with 2 to 4 sound channels plus electrocardiograms and a pulse recording. In most of the recordings the 4 sound channels were used for 2 differently filtered recordings from each of 2 precordial loci.

The Gigli-Muiesan monograph should be useful to Italian-speaking workers in the field of phonocardiography.

VICTOR A. MCKUSICK, M.D.

BOOKS RECEIVED

CIRCULATION is very glad to acknowledge the receipt of the following books. Insofar as space permits, as many appropriate books as possible will be reviewed.

New Methods of Studying Gaseous Exchange and Pulmonary Function. *Alfred Fleisch.* Springfield, Ill., Charles C Thomas, Publisher, 1960, 116 pages, 33 figures. $5.75.

Cardiac Auscultation. Including Audio-Visual Principles. Second Revised and Enlarged Edition. *J. Scott Butterworth, Maurice R. Chassin, Robert McGrath, and Edmund H. Reppert.* New York and London, Grune & Stratton, Inc., 1960, 102 pages, 68 figures. $6.25.

Simposio Sulla Tripsina Chimotripsina. Edited by *W. Montorsi, P. Pietri,* and *A. Peracchia.* Milano, Minerva Medica, 1959, 235 pages, illustrated.

The Microcirculation. Symposium on Factors Influencing Exchange of Substances Across Capillary Wall. Edited by *S. R. M. Reynolds* and *Benjamin W. Zweifach.* Urbana, The University of Illinois Press, 1959, 170 pages, 72 figures. $4.50.

Diagnosis and Treatment of Tumors of the Chest. Sponsored by the American College of Chest Physicians. Edited by *David M. Spain.* New York and London, Grune & Stratton, Inc., 1960, 371 pages, illustrated. $14.75.

Grundriss und Atlas Der Elektrokardiographie. *Rudolph Zuckerman.* Leipzig, Georg Thieme Verlag, 1959, 660 pages, illustrated. D.M. 72.15.

Cancer of the Cervix. Diagnosis of Early Forms. Ciba Foundation Study Group No. 3. Edited by *G. E. W. Wolstenholme* and *Maeve O'Connor.* Boston, Little, Brown & Company, 1959, 114 pages, 27 illustrations. $2.50.

Significant Trends in Medical Research. Ciba Foundation Tenth Anniversary Symposium. Edited by *G. E. W. Wolstenholme, Cecilia M. O'Connor,* and *Maeve O'Connor.* Boston, Little, Brown & Company, 1959, 356 pages, 41 figures. $9.50.

The 20th Century and Your Heart. Arteriosclerosis, Angina Pectoris, Coronary Thrombosis. *Henry J. Speedby.* London, Centaur Press Ltd., 1960, 192, pages. 18s.

Biochemistry of Human Genetics. Ciba Foundation Symposium jointly with the International Union of Biological Sciences. Edited by *G. E. W. Wolstenholme* and *Cecilia M. O'Connor.* Boston, Little, Brown & Company, 1959, 347 pages, 60 figures. $9.50.

The Lifespan of Animals. Ciba Foundation Colloquia on Ageing. Volume 5. Edited by *G. E. W. Wolstenholme* and *Maeve O'Connor.* Boston, Little, Brown & Company, 1959, 324 pages, 58 figures. $9.50.

Your Heart: A Handbook for Laymen. H. M. *Marvin.* Garden City, N. Y., Doubleday & Company, Inc., 1960, 335 pages. $4.50.

Blood Pressure Sounds and Their Meanings. Part 2. Aetiology of Melanotic Cancer. *John Erskine Malcolm.* Springfield, Ill., Charles C Thomas, Publisher, 1960, 70 pages, 14 figures. $3.00.

The Metabolism of Cardiac Glycosides. *S. E. Wright.* Springfield, Ill., Charles C Thomas, Publisher, 1960, 86 pages, 14 figures, 6 tables. $4.75.

Virus Virulence and Pathogenicity. Ciba Foundation Study Group No. 4. Edited by *G. E. W. Wolstenholme* and *Cecilia M. O'Connor.* Boston, Little, Brown & Company, 1960, 114 pages, 13 illustrations.

Metal Binding in Medicine. Edited by *Marvin J. Seven.* Philadelphia, J. B. Lippincott Company, 1960, 400 pages, illustrated. $13.75.

Cardiac Resuscitation. Edited by *J. Willis Hurst.* Springfield, Ill., Charles C Thomas, Publisher, 1960, 141 pages, illustrated. $5.50.

Myocardosis. *Ferdinand Wuhrmann.* Springfield, Ill., Charles C Thomas, Publisher, 1960, 218 pages, 61 figures. $10.50.

Medical, Surgical and Gynecological Complications of Pregnancy. Staff of the Mount Sinai Hospital. Edited by *Alan F. Guttmacher* and *Joseph J. Rovinsky.* Baltimore, The Williams & Wilkins Company, 1960, 619 pages, illustrated. $16.50.

EKG Fibel. *Rolf Heinecker.* Stuttgart, Georg Thieme, Verlag, 1960, 235 pages, illustrated. DM 19.80. $4.70.

A Symposium on pH and Blood Gas Measurement. Methods and Interpretation. Edited by *Ronald F. Woolmer* and *Joy Parkinson.* Boston, Little, Brown & Company, 1960, 210 pages, 48 figures. $8.50.

Pathogenesis and Treatment of Occlusive Arterial Disease. Edited by *Lawson McDonald.* Philadelphia, J. B. Lippincott Company, 1960, 257 pages, illustrated. $5.00.

Electrocardiographic Techniques. Manual for Physicians, Nurses and Technicians. Ed. 2. *Kurt Schnitzer.* New York and London, Grune & Stratton, Inc., 1960, 109 pages. $4.75.

A Primer of Electrocardiography. *George E. Burch and Travis Winsor.* Philadelphia, Lea & Febiger, 1960, 293 pages, 286 illustrations. $5.00.

On the History of Medicine. *Henry E. Sigerist.* Edited by Félix Martí-Ibañez. New York, MD Publications, Inc., 1960, 313 pages. $6.75.

Manual of Blood Morphology. *Lydia Schudel.* Philadelphia, J. B. Lippincott Company, 1960, 52 pages, illustrated, 18 color plates. $4.50.

Pericardita Constrictiva. *T. Teordoreanu.* Bucuresti. Editura Medicala, 1960, 249 pages, 69 figures.

Immediate and Low Level Effects of Ionizing Radiations. Edited by *A. A. Buzzati-Traverso.* London, Taylor & Francis, Ltd., 1960, 381 pages, illustrated.

Leukaemia. Research and Clinical Practice. *F. G. J. Hayhoe.* Boston, Little, Brown & Company, 1960, 335 pages, 12 color plates, 53 figures. $16.00.

Cardiopulmonary Hemodynamics in Chronic Lung Disease with Special Reference to Pulmonary Tuberculosis. Cardiac Catheterization Studies at Rest and on Exercise. *Carsten Müller.* Oslo, Oslo University Press, 1959, 371 pages, 85 tables.

On the Causation of Varicose Veins. Their Prevention and Arrest by Natural Means, An Evolutionary Approach. *T. L. Cleave.* Bristol, John Wright & Sons Ltd., 1960, 39 pages, 1 figure. $2.50.

Electrophysiology of the Heart. *Brian F. Hoffman* and *Paul Cranefield.* New York, McGraw-Hill Book Company, 1960, 323 pages, illustrated. $12.50.

Electron Microscopy of the Cardiovascular System. An Electron Microscopic Study with Application to Physiology. *Bruno Kisch.* Springfield, Ill., Charles C Thomas, Publisher, 1960, 180 pages, 99 figures. $7.50.

Radiation. Use and Control in Industrial Application. *Charles Wesley Shilling.* New York, Grune & Stratton, Inc., 1960, 223 pages, 29 figures. $6.75.

The Heart in Industry. Edited by *Leon J. Warshaw.* New York, Paul B. Hoeber, Inc., 1960, 677 pages, illustrated. $16.00.

The Clinical Use of Aldosterone Antagonists. Edited by *Frederic C. Bartter. Springfield, Ill.* Charles C Thomas, Publisher, 1960, 211 pages, illustrated. $5.00.

Missbildungen Des Menschlichen Herzens. Entwicklungsgeschichte und Pathologie. *Heinz Barthel.* Stuttgart, Georg Thieme, Verlag, 1960, 240 pages, 214 figures. $44.75.

Atlas Der Angiokardiographie Angeborener Herzfehler. *Ralph Kunzler* and *Nikolaus Schad.* Stuttgart, Georg Thieme, Verlag, 1960, 224 pages, 91 figures, $20.25.

ABSTRACTS

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Dimond, E. G., and Benchimol, A.: Phonocardiography in Pulmonary Stenosis: Special Correlation between Hemodynamics and Phonocardiographic Findings. Ann. Int. Med. **52**: 145 (Jan.), 1960.

In 56 patients the diagnosis of pulmonary stenosis was established by cardiac catheterization. The group was composed of 21 patients with isolated pulmonary stenosis, 30 patients with pulmonary stenosis associated with ventricular septal defect, and 5 patients who had pulmonary stenosis with interatrial communication. Phonocardiograms were recorded with simultaneous carotid artery, jugular venous, and electrocardiographic tracings. Isolated moderate and severe pulmonary stenosis usually produced a widely split second sound, with a diminished or absent pulmonic component, prolongation of right ventricular systole, and a systolic murmur that extended through the aortic component of the second sound. If the systolic murmur showed late systolic accentuation, the right ventricular pressure was higher than 100 mm. Hg. In patients with pulmonary stenosis with ventricular septal defect and right-to-left shunt (tetralogy of Fallot), the time of accentuation of the systolic murmur did not show a significant difference from the murmur of isolated pulmonary stenosis. In these patients, the murmur usually stopped at the aortic component of the second sound. The presence of third and fourth sounds indicated marked elevation of the right ventricular pressure. The presence of giant "a" waves in the jugular venous tracing was seen most often in patients with moderate to severe pulmonary stenosis with intact ventricular septum. A systolic ejection click was helpful in the evaluation of the degree of stenosis; it was recorded in only 14 patients with mild and moderate stenosis.

KAYDEN

Eddleman, E. E., Jr., and Thomas, H. D.: The Recognition and Differentiation of Right Ventricular Pressure and Flow Loads. A Correlative Study of Kinetocardiograms, Electrocardiograms, Fluoroscopy and Cardiac Catheterization Data in Patients with Mitral Stenosis, Septal Defect, Pulmonic Stenosis and Isolated Pulmonary Hypertension. Am. J. Cardiol. **4**: 652 (Nov.), 1959.

Thirty-five patients who had right ventricular overloading were studied to determine the value of the kinetocardiogram (ultra-low frequency recording of precordial movements) in distinguishing pressure from flow overloading. All of the 28 patients with pulmonary hypertension or pulmonic stenosis showed a prominent midsystolic outward precordial movement, which was absent in the remaining 7 patients who had atrial septal defects without significantly elevated pulmonary pressures. However, the latter group did have abnormally pronounced early systolic precordial expansion. Thus, all patients had abnormal kinetocardiograms while electrocardiograms were considered to be normal in 29 per cent and right ventricular enlargement was not detected fluoroscopically in 26 per cent. The authors regard the kinetocardiogram and probably precordial palpation as being the most reliable methods of detecting abnormal right ventricular function

ROGER

Eddleman, E. E., Jr., Hughes, M. L., and Thomas, F. D.: Estimation of Pulmonary Artery Pressure and Pulmonary Vascular Resistance from Ultra Low Frequency Precordial Movements (Kinetocardiograms). Am. J. Cardiol. **4**: 622 (Nov.), 1959.

Seventy-four patients with various cardiac conditions were studied by right heart catheterization and by recording precordial movements in the V_1 position. The ratio of the amplitude of initial systolic expansion to subsequent retraction was found to correlate fairly well in most instances with mean pulmonary artery pressure and with pulmonary vascular resistance. The probable effect of pulmonary emphysema, chest wall deformities, or pulmonic stenosis on this correlation was not determined

ROGERS

Effert, S.: Present State of Ultra Sound Cardiography. Arch. Kreislaufforsch. **30**: 213 (Aug.), 1959.

Ultra sound cardiography utilizes the reflection of high frequency sound waves at the interphases of 2 media. A method of recording can be set up in which the excursion is proportional to the distance of the heart wall from the sound generator. A record of cardiac motion with respect to time can thereby be obtained. The motion of the left atrial wall can be accurately observed with this method and delayed emptying, of this atrium as well as slow filling of the left ventricle, can thereby be defined. Such observations were made in 432 patients with mitral valvular lesions and the method was found satisfactory both in preoperative evaluation and postoperative follow-up. Because of special characteristics in wave reflection, tumors or thrombi in the atrium give a characteristic curve, which in 3 patients, could be confirmed at operation. No characteristic excursions of the left atrium were observed in 137 patients with congenital defects. The use of this method in the study of the motion of the great vessels, particularly the pulmonary artery, is still in a stage of development. Pericardial effusion gives a characteristic curve in the fourth interspace.

BRACHFELD

Gaviola, A., and Cabrera, E.: The RR′ Complex in Right Precordial Leads. I. Critical and Historical Examination of the Problem. Arch. Inst. Cardiol. México **29**: 277 (May-June), 1959.

The original concept of incomplete right bundle-branch block (RBBB) was postulated by Wilson in 1921 from the experimental standpoint. It was thought of as a transitional stage between the complete right bundle-branch block and normal activation. In 1947, Wilson proposed an explicit criterion for the diagnosis of incomplete RBBB placing the minimal length of duration of the QRS complex at 0.09 second and not more than 0.12 second; he demanded for this diagnosis also a wide, slurred S wave in lead I and a morphology of the RR′ type in 2 right precordial leads (V_1 to V_E). In 1948, Sodi proposed a clinical criterion for the diagnosis of incomplete RBBB, without the requirement of a certain duration of the QRS complex, although preserving its validity to the slurred S wave in lead I and to the RR′ morphology in V_1. The use of lead V_E was not required. The various clinical criteria proposed as a substitute for that of Wilson did not test the validity of Wilson's criterion nor did they improve its sensitivity and specificity. The work by Miquel and collaborators with a low right intraventricular lead as a more faithful criterion of incomplete RBBB in man, confirms the electrocardiographic criterion of Sodi and the vectorcardiographic criterion of Grishman in a reduced number of cases. With this comparison, it is evident that Sodi's is more sensitive while Grishman's is more specific. The clinical criterion of RBBB postulated by Sodi (1948) should not be confused with his criterion of the intracavity tracings (1947-48). The latter requires an RR′ complex in a low right intraventricular lead and is still considered the most faithful means to reach a diagnosis in both man and in experimental animals.

BRACHFELD

Grant, R. P.: Peri-infarction Block. Progress in Cardiovasc. Dis. **2**: 197 (Nov.), 1959.

Peri-infarction block is an example of a new family of ventricular conduction defects, called the left intraventricular blocks, which are thought to be caused by involvement of 1 of the 2 divisions of the left bundle. The basic features of peri-infarction block are an abnormality of the direction of the initial forces of the QRS interval of a type characteristic of myocardial infarction; an abnormality of the direction of the terminal forces of the QRS interval, so that they come to point opposite to the initial QRS forces; and little or no prolongation of the QRS interval. The change in direction of the mean initial .04 vector in infarction is believed to be due to the loss of electrical activity from the subendocardial layers in the region of the infarct. The superior division of the left bundle runs along the anterolateral surface of the left ventricle and the

inferior division runs along the diaphragmatic surface. Thus, with anterolateral infarction, the superior division may be damaged and excitation would then spread via the inferior division; vectors during the terminal .04 second of the QRS interval would tend to point leftward and superiorly. On the other hand, with diaphragmatic infarction, the inferior division may be damaged and excitation would then spread via the superior division causing the terminal QRS vectors to point inferiorly and slightly rightward. The fact that the 2 divisions of the left bundle extend along the anterolateral and diaphragmatic surfaces of the left ventrical explains why peri-infarction block is seen nearly exclusively with anterolateral and diaphragmatic infarction. Peri-infarction block is thought to be permanent, is seen in 75 per cent of patients with anterolateral infarction, 50 per cent of patients with diaphragmatic infarction and 20 per cent of patients with strictly anterior infarction. There are no prognostic implications of this condition.

KALMANSOHN

Holldack, K., Heller, A., and Groth, W.: The Pericardial Friction Rub in the Phonocardiogram. Am. J. Cardiol. 4: 351 (Sept.), 1959.

Pericardial friction rubs can usually be distinguished from intracardiac murmurs by the following phonocardiographic characteristics: (1) predominance of high-frequency waves, (2) variations in amplitude, (3) appearance in any phase of the cardiac cycle and irregularity of timing, (4) lack of relation to respiration, and (5) transient nature. Presystolic rubs can be separated from presystolic murmurs of mitral stenosis, since the former usually begin earlier and do not extend into the first heart sound. Early diastolic rubs are not decrescendo in nature and thus are distinct from the usual early diastolic murmur. Differentiation of pericardial rubs from systolic murmurs or from pleuropericardial rubs or artifacts by means of sound data alone may not always be possible. The phonocardiogram of 6 rubs are depicted and described.

ROGERS

Kindermann, G.: Extracardiac Influences on the Venous Pulse Curve. Ztschr. Kreislaufforsch. 48: 593 (July), 1959.

In 80 patients the venous pulse in expiratory standstill was registered with the photoelectric method (shadow of paper attached less than 5 cm. above clavicle) together with the heart sounds and electrocardiogram. Termination of the systolic inward movement before the second heart sound or an early notch in this movement was found in 43 per cent of patients with valvular disease and 29 per cent of those with left ventricular failure, but also in 8 per cent of those without heart disease. Normal termination appeared after digitalis, but also after a meal or spontaneously, and premature termination could be produced by Gynergen or bandaging of the extremities. Premature termination of the systolic inward movement alone accordingly does not allow the diagnosis of left ventricular failure but can be brought about also by decreased venous return. A diastolic inward movement showed the same incidence in all groups of patients, while a high presystolic wave was found only in the presence of a prolonged P-R interval.

LEPESCHKIN

Lamb, L. E., Averill, K. H., and Dermksian, G.: Intermittent Right Bundle-Branch Block without Apparent Heart Disease. Am. J. Cardiol. 4: 302 (Sept.), 1959.

Intermittent complete right bundle-branch block was observed in 4 otherwise healthy appearing military officers aged 24 to 39 years. In each instance normal QRS complexes were noted at slower heart rates. Carotid pressure, breathing 100 per cent oxygen, or tilting the patient in various positions seemingly had no effect on intraventricular conduction except that attributable to a change in heart rate. It was suggested that intermittent complete right bundle-branch block, unlike that of the left bundle, may not necessarily indicate organic heart disease.

ROGERS

Lissner, J., and Cordes, R.: On the Range of Variability of the "Normal" Atrial Electrokymographic Curve. Fortschr. Roentgenstr., 91: 494 (Oct.), 1959.

In 83 persons with clinically and radiologically normal hearts the electrokymogram of the right atrium (p.a.) and left atrium (1st diagonal position) was registered together with the electrocardiogram and the carotid pulse. In 23 per cent the curve showed 3 distinct summits, corresponding to the beginning of atrial contraction (A_1), ventricular contraction (S_2) and ventricular diastole (S_6). In 7 per cent the atrial summit dominated the curve and the diastolic inward movement after S_6 was very small; this appeared especially in tachycardia. In 9 per cent the systolic and diastolic summits S_2 and S_6 had approximately equal amplitude, while in extreme cases S_6 dominated. Curves with only 1 summit

were found in 26 per cent. Fusion of both systolic peaks to a single plateau was found in 16 per cent; this configuration could not be attributed to a physiologic mitral insufficiency, as it was found in both the right and the left atrial curves of the same person. It was probably due to systolic rotation of the heart to the left, since it was more common in small, pendular hearts and in lower atrial regions.

LEPESCHKIN

Mürtz, R., and Luster, G.: On the Analysis of the Configuration of Pressure Curves Registered with Intracardiac Catheters. Ztschr. Kreislaufforsh. **48**: 645 (July), 1959.

Registration of pressure through a cardiac catheter and through a wide metal cannula in arterial models and in dogs shows that movement of the catheter at the beginning and end of systole results in resonant oscillations of about 30 cycles per second in the catheter curve. In the undamped catheter these oscillations may exceed the pressure curve in amplitude, and can be reduced when damping is increased by drawing blood into the catheter or air into the pressure transducer chamber or by introducing an artificial stenosis (damping filter) into the catheter. In patients, a filter that reduces the oscillations sufficiently to enable indentification of the pressure pulse also reduces the amplitude of the latter 10 per cent, while a filter sufficient to eliminate the oscillations completely reduces this amplitude 50 per cent. The best compromise was found at a damping resulting in a resonant frequency of 20 c.p.s. However, all damping causes a slower ascent and later summit of the pressure curve and accordingly distorts its true form. Recognition of the latter can be carried out best by registration of both the damped and the undamped curves and comparison of the two.

LEPESCHKIN

Thorburn, G. D., Korner, P. I., and Stephens, J.: The Effect of Volume Dimensions and Type of Flow on the Dispersion of Dye in Normal Dye Curves. Clin. Sc. **18**: 345, 1959.

The authors describe some of the factors in a circulation model that lead to systematic variation in the dispersion of indicator dye apart from the changes produced by variation in the flow and volume of the system. The effect of variations in the over-all dimensions of the volume was studied by alteration of the path length and cross sectional area of the system. The effects of turbulent flow on indicator dispersion were also noted. With flows rates varying from 1 to 4 liters per minute, provided injection and sampling sites were constant and the types of flow approximately similar, the same quantitative relation of variance to flow was found at any level of volume and likewise variance was related to volume in the same manner at any level of flow. Alteration of path length, maintaining the volume between injection and sampling point constant, resulted in systematic differences in the variance at any given flow, the shorter paths and wider cross sections being associated with curves of higher variance. Moreover, it was shown that different segments of the total volume between injection and sampling points could contribute unequally to the final total dispersion of dye. Systematic differences in dye curve variance were also noted when laminar flow was compared to turbulent flow. Thus, dispersion of dye in a model is influenced not only by flow and volume but also by dimensions of the system, type of flow, cross-sectional area, and regional turbulence.

KURLAND

Van Bogaert, A., Van Genabeek, A., Vandael, J., Arnoldy, A., and Van Der Henst, H.: On the Role of the Tissues Surrounding the Heart in the Configuration of QRS in Precordial Leads. Arch. mal. coeur. **9**: 967 (Sept.), 1959.

In dogs in the supine position lead V_4 was taken at the apex beat and the remaining V leads at 3-cm. intervals in a vertical line passing through V_4. With a closed chest, R exceeded S in V_1 but had its maximal amplitude in V_4; S was maximal in V_1 and disappeared in V_4 while Q appeared from V_6 on. Opening of the chest at the midline caused R and S to become smaller and the maximum of R to be displaced toward V_6. Rubber insulation of both ventricles caused P to become taller but QRS to become very small and negative in leads II and III, while QRS became very small and upright in V_{1-4} and inverted in V_{6-8}. If only the diaphragmatic ventricular surface was left free, the voltage was smaller than normal but the precordial leads had the usual configuration. If only 1 point on the ventricular surface touched the chest wall, the configuration was also normal, the maximum potential being found at the point of contact. It was concluded that the precordial leads reflected the potential not of the epicardial region which faced them, but of the points of contact of the heart (especially the ventricular apex) with the chest wall, transmitted through the highly conducting chest wall. If a rubber diaphragm was inserted into a complete incision in the chest wall in the midline, V_1 developed a

deep S wave as in human subjects but if the diaphragm was inserted between V_3 and V_4, V_2 and V_3 developed deep Q waves. The relatively poor conductivity of the lungs was therefore considered responsible for the typical configuration of the precordial leads. If the thorax was made a homogeneous conductor by flooding with serum, QRS became vibratory in all V leads. Many contradictions between anatomic and electrocardiographic findings can be explained by the nonhomogeneous conductivity of the thorax.

LEPESCHKIN

Wyss, S., Schaub, F., and Buhlmann, A.: An Additional Electrocardiographic Criterion on Atrial Enlargement and its Correlation with Hemodynamics. Cardiologia 35: 279, 1959.

The electrocardiograms of 102 patients with known atrial dilatations were compared with those of 100 "normal" control individuals. A new electrocardiographic sign for dilatation or hypertrophy of the cardiac atrium was found by means of standard lead II and measuring the quotient of P-wave duration to P-R interval. The means of this P/PR quotient were 1.49 for normal individuals, 1.23 for patients with a dilated right atrium, and 2.75 for patients with a dilated left atrium. The difference between the means was statistically significant between all 3 groups. The electrophysiologic basis for this new electrocardiographic sign is discussed. There was a good correlation between P/PR quotient and mean left atrial pressure obtained during right-sided cardiac catheterization for patients with left atrial dilatation. No such correlation could be obtained for the right atrium, mainly because of the low pressure readings in this area of the heart.

BRACHFELD

ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Gonin, A., Saint-Cyr, M., Perrin, A., and Froment, R.: Electrocardiographic Evolution of Tuberculous Pericarditis (with the Exception of Chronic Constrictive Pericarditis), Based on 55 Observations and 264 Electrocardiograms. Arch. mal. coeur. 10: 1121 (Oct.), 1959.

Of 33 patients with pericardial effusion showing good reabsorption, the most significant P wave change was a bifid configuration, which disappeared in 14 of the 18 patients after convalescence. Depression of the P-R interval showing regression with convalescence was found in 15 patients. A QRS voltage of less than 5 mm. (true low voltage) was rare, but transient reduction of voltage was found in more than 50 per cent; this depended on the presence of pleural effusion at least as much as on the degree of pericardial effusion. In the acute phase, the S-T elevation never exceeded normal limits and sometimes showed an ascending form without elevation. Inversion of the T wave appeared in all patients; it was usually present in all limb and precordial leads, but in 12 patients it was discordant, with an anterior localization. The changes showed a lag compared to the clinical and radiologic signs, which averaged 3 weeks in patients with an acute onset, and 2 to 3 months in those with a gradual onset; these changes regressed after 2 to 3 months in the former and 5 to 6 months in the latter. Among the 12 patients in whom early constrictive epicardio-pericarditis developed, changes in P-wave configuration appeared in two thirds, and true low voltage in nearly all patients. T-wave inversion was less pronounced but more permanent; discordant T-wave changes (8 patients) all had a posterior localization. Complete disappearance of pericarditis was probable when the sum of the T waves in leads I, II, III, and V_4 exceeded 0.3 mV. Progressive notching of the P wave and persistence of low voltage in spite of disappearance of effusion was an almost certain sign of early constriction, especially if accompanied by hepatomegaly. After pericardectomy the changes in the P and T waves persisted, but low voltage of the QRS complex always disappeared if the operation was successful.

LEPESCHKIN

Knox, J. D. E., and Stuart, A. E.: Acronecrosis and Vascular Fibrinosis in Subacute Bacterial Endocarditis. Scottish M. J. 4: 457 (Sept.), 1959.

A case of subacute bacterial endocarditis of the mitral valve and left atrium is described in which acute heart failure with general "collapse" was associated with the development of cyanosis and necrosis of the tip of the nose and the fourth toe of each foot. Postmortem histologic examination of the involved areas showed the small arteries and veins to be occluded by fibrinous thrombi. There were no signs of mural inflammation, and no intracellular aggregates of organisms were demonstrated in sections stained by Gram's method. There was no evidence of multiple embolic phenomena. It was suggested that compensatory vasoconstriction in the presence of severe heart failure might release tissue thromboplastic substances and precipitate thrombosis.

SHEPS

Re[illegible]ekov, L.: Staphylococcal Endocarditis following Mitral Valvotomy. Lancet 2: 597 (Oct. 1[illegible]), 1959.

[illegible]n cases were collected during a 3-year period of [illegible]aphylococcus endocarditis following 70 consec[illegible]ive mitral valvulotomies. Clinically, the cases dif[illegible]ed little from common subacute bacterial enc[illegible]arditis. The postoperative latent period va[illegible]d from almost none to 4 months. Coagulase neg[illegible]ive staphylococci were easily recovered in 7 c[illegible]ses. The organisms were resistant to penicill[illegible] and somewhat sensitive to streptomycin, tet[illegible]cycline, and chloramphenicol. Erythromycin alo[illegible] or in combination gave the best results. Tre[illegible]tment should continue beyond 6 weeks, perhap[illegible] as long as 6 months, for infection recurs rea[illegible]ily. Three patients died. In 2, infection could not be controlled; in the third, valvular damage resulted in congestive failure.

KURLAND

Scatliff, J. H., Jummer, A. J., and Janzen, A. H.: The Diagnosis of Pericardial Effusion with Intracardiac Carbon Dioxide. Radiology 73: 871 (Dec.), 1959.

The limitations of plain film studies in pericardial effusion are well known. In the last 2 years intracardiac carbon dioxide has been shown to be of definite diagnostic aid in cardiovascular radiology. A series of 22 patients examined by this method is reported. Carbon dioxide is 20 times more soluble in blood than oxygen or air, and this property allows the formation of a transient gas-blood level after intravenous injection of 50 to 100 cc. of the gas. This does not significantly alter the carbon dioxide content of the blood. Rationale of the technic, results, and safety of the method are discussed. The method can be used with rapid filming devices or with the usual equipment of a general radiologic department. It can be performed easily and appears to be without hazard in the cooperative patient. The correlation of the findings in these cases with the clinical course or subsequent autopsy findings would appear to bestow high diagnostic acceptability on the procedure.

KITCHELL

Sch[illegible]ub, F.: On the Prognosis in Subacute Bacter[illegible]l Endocarditis. Cardiologia 35: 316, 1959.

R[illegible]sults among 156 patients with subacute bacter[illegible] endocarditis treated in the period 1947 to 195[illegible] and followed up for 1 to 11½ years were an[illegible]zed. The over-all mortality was 33 per cent. Fif[illegible]en per cent died in the initial phase (2 mo[illegible]hs after initiation of therapy); 15 died with act[illegible]e endocarditis, 11 from myocardial insufficiency, 6 from emboli, 2 from uremia, and 1 with Stokes-Adams syndrome. Thirty patients died at a later stage, of which 27 died with myocardial insufficiency.

SHEPS

Walker, W. F., and Hamburger, M.: A Study of Experimental Staphylococcal Endocarditis in Dogs. I. Production of the Disease, Its Natural History, and Tissue Bacteriology. J. Lab & Clin. Med. 53: 931 (June), 1959.

Perforations of 3-mm. diameter were made in the aortic valves of 33 anesthetized dogs, 4 of which died of ventricular fibrillation on the operating tables, and 6 of which died postoperatively. Of the remainder, 20 were injected at varying intervals with the Harmon strain of *Staphylococcus aureus hemolyticus*, recovered from a human case of acute bacterial endocarditis. Nine dogs failed to develop endocarditis; 11 did develop the disease and became clinically ill 2 to 6 days after a single inoculation of 10^7 to 10^8 staphylococcal cells. The course of the disease resembled that seen in human beings and was rapidly fatal within a few days to 2 weeks. At autopsy, the infected valves showed huge masses of staphylococci usually enmeshed in fibrin with varying degrees of polymorphonuclear reaction. In several hearts, the undersurface of the tricuspid valve presented a "cobblestone" appearance. In most dogs, petechial hemorrhages were found under the epicardium and in the mediastinum. Cultures of the valves yielded 10^9 to 10^{11} staphylococci per gram of tissue. The most striking lesions outside the heart were seen in the kidney, where small red flecks appeared on the surface, extending into the medulla. A few gross renal infarcts were noted. Tissues other than the heart valves yielded only 10^3 to 10^7 staphylococci per gram of tissue. The operative technic was considered by the authors to be a satisfactory one, and they found the induction of endocarditis to be most successful when the operation resulted in a loud aortic diastolic murmur.

MAXWELL

HYPERTENSION

Borhani, N. O.: Use of Trimethidinium Methosulfate (A New Ganglionic Blocking Agent) in the Treatment of Hypertension. Ann. Int. Med. 51: 983 (Nov.), 1959.

Trimethidinium methosulfate is an asymmetric bisquaternary amine with ganglionic-blocking activities but, in addition, has a central component of antihypertensive activity. It was studied in a group of 30 patients with hyper-

tension, all of whom had diastolic levels over 120 mm. Hg, but none of whom was thought to have malignant hypertension. The dose varied from 80 to 240 mg. per day and patients were followed at 2 or 3 week intervals at an outpatient clinic. Although some patients showed no response to the drug, there was an average fall in systolic level of 13.1 mm. Hg and in diastolic level of 5.6 mm. Hg in the recumbent position. The blood pressure showed greater decreases when measured in the upright position. The side effects in order of frequency were dryness of mouth, constipation, paralysis of accommodation, generalized weakness, postural hypotension, and impotence. In contrast to other ganglionic-blocking agents, central nervous system and gastrointestinal complications were not observed. The drug was given only twice a day because of a prolonged duration of activity.

KAYDEN

Cook, J. E., Urich, R. W., Sample, H. G., Jr., and Fawcett, N. W.: Peculiar Familial and Malignant Pheochromocytoma of the Organs of Zuckerkandl. Ann. Int. Med. **52**: 126 (Jan.), 1960.

Although the majority of pheochromocytomas occur in the adrenal glands, 10 per cent are located elsewhere in the body, such as the paraganglia of the sympathetic nervous system. The organs of Zuckerkandl are composed of paraganglionic bodies made up of chromaffin cells located adjacent to the aorta near the origin of the inferior mesenteric arteries. The organs of Zuckerkandl are found easily in infancy but usually disappear by the age of 2 years. This paper presents 3 patients with pheochromocytoma of the organs of Zuckerkandl; 2 of the patients were siblings. Two of the tumors were malignant and 2 were pharmacologically active. Only 3 cases of malignant pheochromocytoma of the organs of Zuckerkandl have been previously reported. In addition to the symptoms of palpitation, excess perspiration, headaches and tachycardia, gastrointestinal complaints were paramount in each of the patients. The diagnosis was confirmed by operation or postmortem examination. In 1 patient widespread metastasis to bone and spinal cord occurred.

KAYDEN

Duffy, J. G., Bond, D. L., and Rogers, S. F.: A New Hypotensive Agent for Toxemia of Pregnancy. J. Obst. & Gynec. **14**: 374 (Sept.), 1959.

Carbethoxysyringoyl methylreserpate (Syrosingopine) was evaluated as a hypotensive agent in 49 patients with toxemia of pregnancy. The most effective method of administration was intramuscularly in a 10 mg. dose repeated in 2 hours if indicated. Excellent response was obtained in 12 of the 30 severely preeclamptic patients, and from 10 of the 12 mildly preeclamptic patients. Good results were observed in 9 of the severe preeclamptic patients. Fair results were reported in 6 of the severe and 2 of the mild preeclamptic patients. Poor results were obtained in only 3 patients with severe preeclampsia. In general the patients who showed no evidence or gave any history of previous toxemia responded best. There were few side effects from Syrosingopine. Two patients experienced severe nasal congestion. Three had mild shaking attacks, and 3 had vomiting after intravenous injection of the drug. In the infants only 1 case of nasal congestion was observed.

KRAUSE

Edwards, F., McKeown, T., and Whitefield, A. G. W.: Arterial Pressure in Men Over Sixty. Clin. Sc. **18**: 289, 1959.

Arterial pressure was studied in 1,723 men over age 60 on the lists of 11 Birmingham general practitioners. In men surviving over 60, mean systolic pressure increased with increasing age, but there was a marked flattening at ages over 70. There was no significant change in mean diastolic pressure over the same age period. Both systolic and diastolic pressures were higher in nonsmokers, mean pressure being inversely related to the number of cigarettes smoked. Mean pressures were higher in drinkers than in nondrinkers, but no relation was found to physical or mental demands of occupation. In men aged 60 to 69, pressures were higher in unskilled and partially skilled classes, but over age 70 these did not differ from those of the professional occupations.

KURLAND

Freed, S. C., and St. George, S.: Myocardial Sodium and Potassium Content in Relation to Blood Pressure. Am. J. Physiol. **197**: 214 (July), 1959.

In rats made hypotensive through potassium deprivation, there was a slight loss in myocardial potassium but a significant increase in sodium content. Previous studies had shown that under similar experimental conditions the potassium content of the aorta was lowered but the sodium content was unchanged. Restoration of blood pressure following cortisone or prednisone administration was associated with removal of the

exce[illegible] myocardial sodium. The administration of 9 al[illegible]a-fluorohydrocortisone did not restore the bloo[illegible] pressure, and only partially reduced the sodi[illegible]n content, but did decrease further the potass[illegible]n content. This resulted in an unchanged sodi[illegible]:potassium ratio. Desoxycorticosterone acetate [illegible]owered the blood pressure with a higher sodi[illegible]:potassium ratio of the myocardium thro[illegible]h a decrease in potassium and an increase in s[illegible]ium contents. The authors suggest that the effic[illegible]y of the corticosteroids in treating the refrac[illegible]ry edema of congestive heart failure may be d[illegible]e to the mobilization of sodium from the myo[illegible]rdium and aorta and improvement in cardiac [illegible]emodynamics.

KAYDEN

Gifford, R. A., Jr.: Treatment of Hypertension with Trimethidinium Methosulfate—A New Ganglion-Blocking Drug. Proc. Staff Meet., Mayo Clin. **34:** 481 (Sept. 30), 1959.

Trimethidinium methosulfate (in this study 20-mg. tablets of Ostensin) is an asymmetric bisquaternary amine that acts as a ganglionic-blocking agent. Its use is reported in the treatment of 13 hypertensive patients for periods ranging from 6 weeks to 17 months. In 3 patients the blood pressure was not reduced but in these patients the drug was not pushed to the limit of tolerance. Side effects of ganglionic-blockade were produced in 10 patients and 3 patients discontinued the medication on this basis. However, of 9 patients who previously were on other ganglionic-blocking agents, 6 preferred trimethidinium because it produced fewer or less severe side effects or controlled hypertension better with no greater side effects.

KRAUSE

Gitlow, S. E., Mendlowitz, M., Khassis, S., Cohen, G., and Sha, J.: The Diagnosis of Pheochromocytoma by Determination of Urinary 3-Methoxy, 4-Hydroxymandelic Acid. J. Clin. Invest. 39: 221 (Jan.), 1960.

In normal human urine 3-methoxy, 4-hydroxymandelic acid, also referred to as vanillylmandelic acid, has been identified as a metabolite of the catecholamines epinephrine and norepinephrine. This paper describes a paper chromatographic method of identifying and measuring the vanillylmandelic acid in human urine. The values obtained in 30 subjects with proved pheochromocytoma are compared with the values in 15 normal subjects and in 36 patients with primary hypertension. The urinary vanillylmandelic acid excretion of patients with pheochromocytoma varied from 6.0 to 40 μg. per mg. of creatinine, and averaged 10 times the urinary norepinephrine plus epinephrine content (per mg. of creatinine). In normal subjects the urinary excretion of vanillylmandelic acid varied from 0.8 to 2.0 μg. per mg. of creatinine and in patients with primary hypertension the values were from 0.7 to 3.0 μg. per mg. of creatinine. The amount of vanillylmandelic acid excreted in the normal and hypertensive subject was about 100 times the amount of norepinephrine plus epinephrine content of the urine. This method is proposed as a helpful laboratory determination in the diagnosis of pheochromocytoma.

KAYDEN

Harington, M., Kincaid-Smith, P., and McMichael, J.: Results of Treatment in Malignant Hypertension. Brit. M. J. **2:** 969 (Nov. 14), 1959.

The results of treatment are reviewed in 82 patients with malignant hypertension, 81 of whom had papilledema. Fifty six patients died and of these 42 were autopsied. Renal arterial occlusion was present in 8.5 per cent. The ganglionic-blocking agents used were hexamethonium, pentolinium, and mecamylamine—with or without reserpine. A control untreated group was available. In the treated group the over-all survival rate was 50 per cent at 1 year, 33 per cent at 2 years, and 25 per cent at 4 years as compared with a 90 per cent mortality in the first year in the untreated group. Expressed in other words, treatment increased life expectancy by a factor of 6 to 8 times that expected from a control series. Prolonged survival was particularly evident in patients with normal or only minimally impaired renal function at the start of therapy. Heart failure as a cause of death was especially decreased by treatment and when death did occur it was usually due to renal failure. Retinitis and electrocardiographic improvement were common but a reduction in heart size was not particularly evident. When the blood urea nitrogen was 80 mg. per 100 ml. or less, renal function was usually improved or remained stationary; above this value progressive deterioration was the rule. Neurologic complications did not improve with treatment. Kidney section studies also revealed that after treatment with hypotensive drugs the main changes were a conversion of cellular intimal hyperplasia in the interlobular arteries to fibrous intimal thickening and a "healing" of fibrinoid degeneration to hyaline and fibrous tissue.

KRAUSE

Hulet, W. H., and Smith, H. W.: Negative Pressure Respiration, Water Diruresis and Natriuresis in Normotensive, Hypertensive and Prehydrated Normotensive Subjects. J. Clin. Invest. 38: 1972 (Nov.), 1959.

The effect of negative pressure breathing (NPB) on sodium, total solute, and water excretion was observed in hydropenic normotensive subjects, hydropenic hypertensive subjects, and normotensive subjects who had been prehydrated by water loading 8 to 9 hours before NPB. Normotensive and hypertensive subjects responded to negative pressure breathing with increased urine flow primarily because of increased free water clearance. Significant increases in sodium excretion did not occur. NPB in prehydrated subjects induced a substantial increase in free water clearance, though at the time of NPB the subjects were in an antidiuretic state comparable to hydropenic prehydrated subjects. A small increase in sodium excretion was thought to be due to dead-space error. Under the conditions of this study the authors suggest that negative pressure breathing is not a stimulus that leads to excessive natriuresis in subjects (hypertensive and prehydrated) otherwise predisposed to natriuresis.

KAYDEN

Janney, J. G., Jr., Caciolo, C., Duane, G. W., Reddy, S. R. V., and Simonidis, A. K.: Clinical Evaluation of Trimethidium Methosulphate. A New Ganglioplegic Agent. Am. J. Cardiol. 4: 745 (Dec.), 1959.

The effects of administering trimethidium methosulfate, in average daily doses of 334 mg. given in 2 or 3 portions orally, were observed over a mean period of 8 months in 20 essential hypertensive patients. The hypertension was moderate in most patients. Other medications, excepting ganglioplegic agents, were continued. Substantial blood pressure lowering was noted in 15 patients, and 11 became normotensive in the erect position. Most had previously responded to pentapyrrolidinium therapy. The hypotensive effect was generally well maintained during months of therapy, although in 2 patients the dosage of trimethidium had to be increased. Side effects from trimethidium were quite common; 8 patients required neostigmine at least once daily for constipation, but this became less bothersome as time went by. Comparison with therapeutic results reported for other long-acting ganglioplegic agents showed blood pressure control to be as good or better and the side effects to be less troublesome when trimethidium was used.

ROGERS

Johnson, J. M., and Lewis, J. A.: The Effects of Amphenone on Renal Function in Hypertensive Subjects before and after Acute Reduction of the Blood Pressure. Canad. M. A. J., 82: 130 (Jan. 16), 1960.

Hexamethonium-induced lowering of the blood pressure to normal or near normal levels in 4 hypertensive patients was followed by pronounced decreases in urine sodium, chloride, and water excretion—effects that previously had been thought possibly due to increased mineralocorticoid activity. However, similar urinary responses to hexamethonium-induced normotension were observed following pretreatment for 24 hours with 5 to 10 Gm. of amphenone, an adrenal-suppressing agent. Therefore, it was believed that factors other than adrenal steroid activity were of importance in influencing the antidiuresis and antinatriuresis attending blood pressure reduction.

ROGERS

Lin, T. Y., Hung, T. P., Chen, C. M., Hsu, T. C., and Chen, K. P.: A Study of Normal and Elevated Blood Pressures in a Chinese Urban Population in Taiwan (Formosa). Clin. Sc. 18: 301, 1959.

This is the first of a series of epidemiologic studies in Taiwan with the aim of ascertaining the prevalence of high blood pressure in a Chinese urban population through an intensive field survey. All the apparently healthy people over the age of 15 in 2 districts of Taipei were chosen for investigation; this included 6,421 men and 3,308 women. The means of systolic pressure of both males and females were fairly level at younger ages, but a steady rise began at ages 40 to 44 in men and 35 to 39 in women. The diastolic pressures showed a similar tendency. There was an increasing variability of blood pressure with age. Young men had significantly higher mean blood pressure than women, but the difference in systolic pressures did not continue after ages 35 to 39 and in diastolic pressures did not continue after ages 30 to 34. Taiwanese had higher systolic blood pressures than mainlanders but the diastolic pressure was higher only in Taiwanese women. A comparison with studies in America and Britain showed that the Chinese generally had lower systolic and diastolic pressures in the younger age groups, but that the pressure rise in the Chinese in early middle age minimized the differences from the Occidentals thereafter.

KURLAND

Meltzer, L. E., Eichner, L. G., Ural, E., and Kitchell, J. R.: A Comparison of Hydrochlorothiazide and Chlorothiazide in the Treatment of Hypertension. Am. J. Cardiol. 4: 741 (Dec.), 1959.

Hydrochlorothiazide, 50 to 200 mg. daily, was substituted for chlorothiazide, dose not stated, in the therapy of 60 stabilized essential hypertensive patients over a 12-week period. A blood pressure reduction of 10 per cent or more was observed in 27 (45 per cent) of the whole group and in 68 per cent of the apparently more severe cases who were receiving ganglionic-blocking agents. Of 12 previously untreated hypertensive patients, the administration of hydrochlorothiazide alone, 50 to 200 mg. daily, was followed within 2 weeks by a significant blood pressure reduction in 8 patients; but this effect was sustained for 10 weeks in only 3 of these patients. A comparison of the diuretic effects of hydrochlorothiazide, 150 mg. daily, and chlorothiazide, 2,000 mg. daily, in other patients showed the former agent to produce a 12 per cent greater excretion of sodium, a 28 per cent greater excretion of chloride, and a 2 per cent lesser excretion of potassium. It is concluded that hydrochlorothiazide has a slightly greater hypotensive effect than chlorothiazide, which is believed to be related to its superior saluretic action.

ROGERS

Moyer, J. H., and Brest, A.: Untreated and Treated Patients with Hypertension. Dis. Chest. 36: 297 (Sept.), 1959.

Since the kidney is one of the most sensitive organs to vascular changes resulting from hypertension, the effects of hypertension on this organ in patients with elevated blood pressure and the effects of elevated blood pressure reduction were studied. These findings were compared with those made on a similar group of patients who received no antihypertensive therapy for a period of 3 to 5 years. In 129 patients who had not been treated previously for hypertension, the glomerular filtration rate, as estimated by the inulin clearance, was plotted against the direct intra-arterial pressure. The higher the pressure, the lower was the filtration rate. Over-all vasoregulator mechanisms were similar in normotensive and hypertensive individuals, but in the latter, the outflow of vasoconstrictor impulses was increased or the responsiveness of the blood vessel was increased above normal. Generally, reserpine given parenterally was the initial drug for the treatment of emergency states of severe essential hypertension. When this was not adequate, a ganglionic-blocking agent (preferably hexamethonium because of its shorter duration of action) or a parenterally administered veratrum preparation should be used. For ambulatory treatment, the most important aspects were the suppression of sympathetic impulses from the brain to the blood vessels and depletion of body stores of sodium. Rauwolfia or a derivative was preferred as a sympathetic depressant. It was given in combination with chlorothiazide, and if the patient did not respond adequately within one month, he also received a ganglionic-blocking agent, used with precautions to minimize the severe side reactions. Reduction of blood pressure with antihypertensive drugs in patients with malignant or nonmalignant hypertension arrested the vascular degeneration associated with severe forms of the disease.

MAXWELL

Page, I. H., and Dustan, H. P.: A New Potent Antihypertensive Drug. J.A.M.A. 170: 1265 (July 11), 1959.

The antihypertensive effects of orally administered guanethidine were studied in 18 patients hospitalized for hypertensive cardiovascular disease. This drug seemed to be an effective hypotensive agent with mild diarrhea as the only side effect noted. Blood pressure drop was slow, prolonged, and often accompanied by postural hypotension. Bradycardia was common. The chemical structure and mechanisms of action of this drug differ from those of other antihypertensive agents. The dosage in these patients ranged from 25 mg. every other day to 150 mg. 3 times daily. Laboratory tests showed that injections of guanethidine modified the responses in animals to subsequent injections of either pressor or depressor drugs.

KITCHELL

Palmer, R. S.: Treatment of Hypertension: A 23-Year Follow-up of 453 Patients with a Selected Review and Report of Current Experience. J. Chron. Dis. 10: 500 (Dec.), 1959.

This paper represents the fourth and final report on 453 patients with hypertension who were treated medically. The majority were seen in the years 1935 to 1940. No new patients were admitted to the series since 1941, and there are now 79 survivors. The classification used was as follows: grade I, hypertension without recognized organic changes or functional failure; grade II, no functional failure, but with organic changes in 1 or more of the 3 vital areas (head, heart, or kidneys); grade III, organic change plus func-

tional failure in 1 or more vital areas; and grade IV, the clinical syndrome of malignant hypertension. In grades I and II, it is safe, cheap, and often possible to control the blood pressure level by diet plus phenobarbital. However, drugs meet easier acceptance by patients than restriction in diet. *Rauwolfia serpentina* and its derivatives are slightly more effective than phenobarbital and have more side effects. Chlorothiazide is a substitute for salt restriction. Its use is recommended combined with small doses of ganglion-blocking agents in grade III patients with actual or threatened congestive heart failure and used alone in less severe grades with high blood pressure levels. Every resource of diet and drugs is required to control the blood pressure level in grade IV hypertensives. Cardiovascular-renal disease is the cause of death in 75 to 90 per cent (as compared with 50 per cent for the general population) and appears earlier in life with each rise in grade.

MAXWELL

Paterson, J. C., Mills, J., and Lockwood, C. H.: The Role of Hypertension in the Progression of Atherosclerosis. Canad. M. A. J. **82**: 65 (Jan. 9), 1960.

The severity of atherosclerosis in 184 autopsied hospital patients aged 50 to 84 years was estimated by measuring the total extractable lipid content of the intimas of coronary, cerebral, and femoral arteries and of the distal aorta. Significantly higher intimal lipid values were found in the 3 arteries excepting the aorta of patients having systolic blood pressures of 150 mm.Hg or higher and in those patients with systolic hypertension plus consistent diastolic hypertension of 95 mm.Hg or more. Similar ages and serum cholesterol levels were found for the hypertensive and the normotensive subjects. It was believed that hypertension had promoted atherosclerosis and that the mechanism might have been an increased tendency for intimal rupture and hemorrhage with consequent enhancement of atherogenesis.

ROGERS

Rapaport, A., Evans, B. M., and Wong, H.: Some Short-Term Metabolic Effects of Chlorothiazide in Hypertensives on a Rice Diet. Canad. M. A. J. **81**: 984 (Dec. 15), 1959.

Eight hypertensive nonedematous adults and 2 normal subjects were given a rice diet during a week of hospitalization for study. One gram of chlorothiazide was ingested on each of the last 4 days by the hypertensive patients and by 1 of the normal subjects. The drug appeared to cause a slight decrease in serum sodium, chloride, and potassium levels consequent to moderate increase in urinary excretion of these ions. These changes were attributed to the effect of chlorothiazide on the renal tubules, since glomerular filtration rate diminished. Carbonic anhydrase inhibition also was evident from increased urinary bicarbonate and decreased urinary citrate outputs. Among the hypertensive patients, other changes noted were reduction in plasma volume and in total exchangeable sodium and increased hematocrit values; there was a slight reduction in blood pressure, part of which occurred before chlorothiazide was given.

ROGERS

Robinson, R., Ratcliffe, J., and Smith, P.: A Screening Test for Phaeochromocytoma. J. Clin. Path. **12**: 541 (Nov.), 1959.

It has been shown that epinephrine and norepinephrine are metabolized to 3-methoxy 4-hydroxy mandelic acid or vanillylmandelic acid. In pheochromocytoma this latter substance is excreted in greater than normal quantities. A fairly rapid 2-dimensional paper chromatographic method for semi-quantitative measurement of vanillylmandelic acid in urine is described. Urines are collected over a measured period of time. It is best to have the subject avoid bananas, coffee, and citrus fruits. He should also be free of undue stress during the period of collection. In this study, urine specimens were collected from 4 proved cases of pheochromocytoma, from 100 cases of essential hypertension, and from 30 normal subjects. Urine samples collected from normal subjects showed a consistent range of values in excretion of vanillylmandelic acid. Urine from patients suffering from pheochromocytoma revealed levels of excretion ranging from 5 to 7 times those in normal controls. After removal of the tumors in 3 of the patients, the urine showed a marked fall in vanillylmandelic acid excretion in 2 patients, but a persistent high excretion in the third.

MAXWELL

Rosenfeld, J. B., Beem, J., Brest, A., and Moyer, J. H.: Observations on Flumethiazide in the Treatment of Essential Hypertension. Am. J. Cardiol. **4**: 734 (Dec.), 1959.

The effects of administering flumethiazide, 500 mg. twice daily, or whole Rauwolfia, 50 to 100 mg. twice daily or both were observed over a 4-month period in 34 clinic patients having mild hypertension. Substantial lowering of the blood pressure

in the supine position was obtained in 41 per cent of those receiving flumethiazide, in 24 per cent of those on Rauwolfia, and in 50 per cent of those taking both drugs. A slightly higher portion of each group had a similar degree of hypertensive effect when measured in the upright position, and 59 per cent of those on combined treatment became normotensive when upright. The mode of hypotensive action of flumethiazide was presumed to be the same as that of chlorothiazide, namely by producing sodium diuresis with decrease in plasma volume. No serious side effects were encountered although several patients complained of mouth dryness or digestive disturbances, and in a single instance slight hypokalemia was found.

ROGERS

Slater, R. J., Geiger, D. W., Azzopardi, P., and Webb, B. W.: Hypertension in Children. Canad. M. A. J. **81**: 71 (July 15), 1959.

The clinical and pathogenetic aspects of arterial hypertension in children are reviewed, and 8 illustrative case reports are presented. Hypertension in the child is uncommon and is likely to be overlooked. It is most often due to renal disorders, especially glomerulonephritis. Other known causes are the same as those in the adult, except that Wilm's tumor and coarctation of the aorta are almost confined to children. Aldosteronism has not yet been found in a child but case number 7 had increased aldosterone urinary excretion; the adrenal glands, although normal in appearance, were removed and normotension ensued. Essential hypertension is rare in children. Before making this diagnosis, thorough investigation is needed, occasionally including individual renal function studies, aortograms, and tests for pheochromocytoma or for plumbism. Treatment of the hypertension per se is best carried out with the usual hypotensive drugs.

ROGERS

Tobian, L., Janecek, J., and Tomboulian, A.: The Effect of a High-Sodium Intake on the Development of Permanent Nephrosclerotic Hypertension. J. Lab. & Clin. Med. **53**: 842 (June), 1959.

The incidence of permanent "nephrosclerotic" hypertension was not increased by a high-sodium intake in experiments performed on rats. Hypertension was produced by partial constriction of 1 renal artery by means of a clip. When the ischemic "clipped" kidney was not excised until 6 months later, hypertension persisted indefinitely in 2 per cent of the rats that drank only 1 per cent saline during the 6-month interval and in 43 per cent of the rats that drank only tap water for the same period. The granulation of the renal juxta-glomerular cells in the remaining kidney of rats with this permanent hypertension was also compared with the granulation in rats whose blood pressure remained normal after "clipping" or returned to normal after excision of the "clipped" kidney. The index averaged 8.5 in the permanent hypertensive rats drinking only tap water, 18.3 in those remaining normotensive after "clipping," and 18.6 in the lone kidney of those in which hypertension disappeared following excision.

MAXWELL

Vertes, V., and Sopher, M.: Clinical Studies on Hydrochlorothiazide-Antihypertensive and Metabolic Effects. J.A.M.A. **170**: 1271 (July 11), 1959.

Hydrochlorothiazide, a potent diuretic as well as an antihypertensive agent, exerts an effect by producing sodium and chloride diuresis. Ten patients with essential hypertension and 1 with congestive heart failure were given 50 mg. of hydrochlorothiazide 3 times a day. The hypertensive patients experienced a fall in pressure and the patient with edema had a diuresis. The drug was well tolerated and no major toxic effects were noted. It is suggested that the best way to regulate blood pressure in essential hypertension is to admit the patient to the hospital, place him on a no-sodium diet for several days until his sodium stores are depleted, and then give him a general diet along with a drug such as hydrochlorothiazide to maintain the low sodium state.

KITCHELL

PATHOLOGY

Buck, R. C.: Electron Microscopic Observations on Capillaries of Atherosclerotic Aorta. Arch. Path. **67**: 656 (June), 1959.

The evaluation of capillaries located in the tunica intima of atheromatous arteries has been made easier, since the resolution provided by the electron microscope makes possible the positive identification of capillaries and of interstitially located capillaries. This assumes importance since it is believed by some that by producing small hemorrhages in the arterial intima, the capillaries have a bearing on the genesis and progression of the atheromatous change, or by their rupture in the terminal stages of the sclerotic process they may produce sufficient subendothelial hemorrhage to occlude a coronary artery. The capillaries in a human aorta were studied by electron microscopy.

They were seen to have the usual structure of capillaries in other sites. Extravasated red blood cells were seen. In this 1 case, the observations provided no bearing on the etiology of atherosclerosis.

MAXWELL

Gillman, T.: Reduplication, Remodeling, Regeneration, Repair, and Degeneration of Arterial Elastic Membranes. Arch. Path. 67: 624 (June), 1959.

Some implications for the pathogenesis of arterial disease are discussed. The description of microscopic changes, associated with very early intimal lesions and especially reduplications of vascular elastic membranes (VEM), are presented for human arteries at different ages. Even in infants alterations were encountered in the morphology and staining reactions of arterial internal elastic membranes. In the discussion, comment was made that evidence indicates that, contrary to general opinion, intimal fat deposits may not be primary, that they may actually be antedated by subtle changes in the endothelium, ground substances, or other intimal components and that these preliminary changes may then predispose to localized lipid accumulations, which in turn may be further facilitated by hemodynamic factors, the state and concentration of blood lipids, etc. Regeneration, remodeling, and repair of VEM is associated with mucopolysaccharide accumulation, either around affected VEM or in the intima, with or without increased cellularity and lipids and the formation of new reticulin or collagen fibers. It was suggested that a distinction could be made between the pathogenesis of arterial lesions characteristic of the fourth and fifth decades of life and senile sclerosis, the latter being due in large measure to a slow deterioration with aging of the normal regenerative processes into repair with consequent gradual vascular fibrosis.

MAXWELL

PHARMACOLOGY

Atkinson, M.: The Effect of Diuretics on Portal Venous Pressure. Lancet 2: 819 (Nov. 14), 1959.

The effectiveness of diuretics in controlling ascites has been demonstrated, but the mechanism of action is uncertain. The present study investigated the influence of diuretics on portal venous pressure and plasma colloid osmotic pressure. Intrasplenic pressure, measured by splenic puncture, was used as a measure of portal venous pressure and estimation of serum protein levels was used to detect changes in plasma colloid osmotic pressure. Ten patients with portal cirrhosis were investigated while undergoing treatment for ascites. The clinical response to treatment was satisfactory in 6 patients, and in each diuresis occurred; ascites decreased and weight fell. Little change in serum protein levels was noted during treatment; the total protein of ascitic fluid showed little alteration by treatment with diuretics. This suggests that the colloid osmotic gradient across the capillary walls was unaffected by treatment with diuretics. Intrasplenic pressure fell during 10 of 11 periods of treatment. In general, the patients with a satisfactory clinical response showed a greater reduction in intrasplenic pressure. All the patients in whom ascites was not lost showed greater pressures after treatment. It was shown by measurement after paracentesis that reduction in intra-abdominal tension after decrease of ascitic fluid could not account for the reduction in intrasplenic pressure caused by diuretics. Measurements after a single dose of chlorothiazide showed that the fall in intrasplenic pressure was related to the diuretic response. It is suggested that the principal mechanism by which diuretics relieve ascites is by reduction of portal venous pressure.

KURLAND

Dupasquier, E., and Reubi, F.: The Effects of Iproniazid on Blood Pressure and Renal Hemodynamics. Cardiologia 35: 256, 1959.

Ten patients suffering from angina pectoris and 3 others were treated with iproniazid (up to 150 mg. daily). The effect of the drug was compared with that of a placebo. The response to iproniazid was generally evident 3 to 20 days after the start of treatment and lasted 5 to 20 days after the drug was replaced by placebo. Iproniazid relieved pain in 40 per cent of anginal cases and reduced it in 50 per cent. The electrocardiogram was not altered. The placebo had no appreciable effect. Significant side effects were observed in 70 per cent of the patients. The arterial systolic pressure fell on an average by 11.3 per cent and the diastolic by 12.4 per cent. Renal function tests were carried out in 11 patients both before and 3 to 4 weeks after the start of treatment. There was an average drop of 12.1 per cent in glomerular filtration and of 9.1 per cent in renal plasma flow. These changes in renal hemodynamics showed a striking correspondence with the fall in arterial blood pressure.

BRACHFELD

Fr[illegible]h, A., and Birnbaum, L.: Decelerator and Antiarrhythmic Properties of Amotriphene. J. Pharmacol. & Exper. Therap. **127**: 128 (Oct.), 1959.

Comparisons were made of the effect of amotriphene, quinidine, and procaine amide on the refractory period and conduction velocity of the isolated atrium of the rabbit. Amotriphene was about 4 times more effective than quinidine and 8 times more effective than procaine amide on increasing the refractory period. Amotriphene and quinidine were equally effective in decreasing conduction velocity. Amotriphene had powerful decelerator properties, on both normal and epinephrine-stimulated isolated rabbit atria and on normal and epinephrine-stimulated sinus rates of the anesthetized dog. There was little effect on epinephrine-induced changes in cardiac contractility and hypertension. In experimentally induced atrial flutter and fibrillation amotriphene slowed the atrial and ventricular rate and produced a reversion to normal rhythm.

SHEPS

Jick, S., and Karsh, R.: The Effect of Calcium Chelation on Cardiac Arrhythmias and Conduction Disturbances. Am. J. Cardiol. **4**: 287 (Sept.), 1959.

Cardiac arrhythmias or conduction disturbances in 27 patients were treated by infusing intravenously 3 Gm. of sodium versenate in 400 ml. of 5 per cent glucose solution over a 30-minute period. Immediately after the infusion, the serum calcium level had fallen 0.4 to 2.5 mg. per cent in all patients tested; and in all except 2 a slight decrease in serum potassium was found. The infusions were well tolerated except for mild aching of the infused arm and lip tingling. In each of 11 instances of digitalis intoxication, a pronounced response occurred, usually toward the end of the infusion; the effect continued for periods up to 1 hour or, infrequently, longer. The response consisted of marked reduction in number of ventricular premature beats in 3 patients, a shortening of the prolonged P-R interval in 2, reversion of atrial tachycardia with block to sinus rhythm in 4, a slowing of atrial and ventricular rates in 1 instance of atrioventricular dissociation, and a conversion of bidirectional tachycardia to atrial fibrillation in 1 patient. In 15 patients not definitely intoxicated by digitalis, only 1 showed a decided response, namely a disappearance of ventricular premature beats. The results suggest that sodium versenate administration may be useful in distinguishing and treating those arrhythmias due to digitalis overdosage.

ROGERS

Lee, W. C., and Shideman, F. E.: Mechanism of the Positive Inotropic Response to Certain Ganglionic Stimulants. J. Pharmacol. & Exper. Therap. **126**: 239 (July), 1959.

This paper deals with the nature of the stimulant action on the myocardium of tetramethylammonium (TMA) nicotine, and acetylcholine. These agents produce a transitory positive inotropic effect, in the presence of atropine, on isolated papillary muscles and atrial preparations of the cat and on the heart in the heart-lung preparation of the dog. Following this response the myocardium was refractory to the same drug or the other 2 that were studied. The positive inotropic effects of all 3 drugs were inhibited by ganglionic-blocking agents (hexamethonium, tetraethylammonium, and tubocurarine). However, histologic examination of serial sections of papillary muscles that responded to the positive inotropic action of TMA, nicotine, or acetylcholine, failed to reveal the presence of ganglion cells, suggesting that the cardiostimulant activity of these substances was not dependent on the presence of ganglia. Cocaine and ephedrine inhibited the positive inotropic response of the atropinized papillary muscle of the cat to either TMA or epinephrine. Intravenous injection of choline 2:6-xylyl ether bromide in the dog, blocked the cardiac responses to stimulation of postganglionic sympathetic nerves but not to vagal stimulation or epinephrine injection. This choline derivative also blocked the positive inotropic response of the papillary muscle to TMA or nicotine, but not to epinephrine or norepinephrine. After the administration of dichloroisoproterenol, TMA, or nicotine, as well as epinephrine or norepinephrine, failed to produce their usual positive inotropic response. The intravenous administration of reserpine (0.5 to 5.0 mg./Kg.) to cats markedly reduced the myocardial content of catecholamines within 20 hours. Papillary muscles and atria from these cats exhibited little or no positive inotropic response to either TMA or nicotine, but responded markedly to epinephrine or norepinephrine. Myocardial catecholamines in cats were reduced by almost 80 per cent within 15 to 26 days following bilateral removal of the sympathetic innervation to the heart. Atria and papillary muscles from these animals still exhibited a positive inotropic response to TMA or nicotine in the presence of atropine, but the responses were significantly less than those of similar preparations from nonsympathectomized animals. There appear to be 2 possible explanations for the above findings: the cardiostimulant action of TMA, nicotine, or acetylcholine is mediated via stimulation of postganglionic sympathetic nerve

endings; there exist in the heart certain elements that do not possess the morphologic characteristics of ganglia but that behave pharmacologically as if they were and that TMA and certain ganglionic stimulants may act directly on these elements to liberate epinephrine-like substances.

RINZLER

Levy, B.: Adrenergic Blockade produced by the Dichloro Analogs of Epinephrine, Arterenol and Isoproterenol. J. Pharmacol. & Exper. Therap. **127**: 150 (Oct.), 1959.

The intestinal inhibitory responses in the dog produced by isoproterenol were blocked by dichloro-isoproterenol (DCI). A similar response was seen after Win277, Win3046, and nylidrin. The depressor responses to these drugs were reduced by pre-treatment with DCI. The dichloro analogs of epinephrine (DCE) and arterenol (DCA) produced lesser effects. The intestinal inhibitory responses produced by epinephrine and levarterenol were not reduced by DCI, DCE, or DCA. The pressor responses were slightly prolonged after DCI but were not significantly altered after DCE or DCA. DCI reduced the intestinal inhibition produced by Butanephrine and when Dibozane was added there was complete abolition of intestinal inhibition. The depressor response to Butanephrine was converted to a pressor response after DCI and after Dibozane was converted back to a depressor response. Dibozane completely abolished the intestinal inhibition produced by methozamine, metaraminol, Paredrine, and ephedrine, but not by DCI. The pressor responses to these drugs were not significantly altered after DCI. It is suggested that this evidence supports the theory that the inhibition of intestinal motility produced by adrenergic agents acts through 2 different receptors.

SHEPS

Madan, B. R., and Sharma, V. N.: Serpentine and Ajmaline in Ventricular Ectopic Activity. Arch. int. pharmacodyn. **122**: 323 (Nov.), 1959.

Serpentine (3.5-8 mg. per Kg.) and ajmaline (5-8 mg. per Kg.) were tested for their antiarrhythmic activity in ventricular irregularities induced in dogs by a 2-stage coronary ligation. Serpentine was successful in completely suppressing the ectopic beats in 5 out of 8 experiments, whereas ajmaline fully restored sinus rhythm in 2 out of 7 dogs. However, total heart rate was reduced with diminution in the intensity of arrhythmia in all the cases. The doses employed in these experiments were devoid of any serious toxic manifestations. It is suggested therefore that these 2 alkaloids of Rauwolfia serpentina may be tried clinically.

BRACHFELD

McKendrick, C. S., and Godfrey, A. M.: Acetylcholine, Adrenaline, and the Heart. Lancet **2**: 482 (Oct. 3), 1959.

The isolated rabbit atrium was used to ascertain whether the catecholamines, epinephrine, and norepinephrine, play a part in the initiation and control of myocardial contraction. Acetylcholine, .01 microgram per 50 ml. of Locke's solution, stopped the actively beating atrium. If the atrium stopped naturally or after proguanil, acetylcholine started it. Both .01 microgram of epinephrine and norepinephrine restarted the atrium arrested by fatigue or proguanil and also the atrium that had been inhibited by acetylcholine. Several adrenolytic agents all stopped the beating atrium. When the atria were stopped by these agents, they could not be revived by washing or by acetylcholine, but they could always be restarted by the catecholamines. Acetylcholine antagonists hyoscine and tubocurarine failed to stop the atrium, but atropine in large dosage gradually caused the atrium to stop. After atropine arrest, acetylcholine would inconsistently restart the atrium, but epinephrine and norepinephrine effectively restarted it each time. Mecamylamine in large dosage stopped the atrium. Acetylcholine restarted it half the time, but the catecholamines did so invariably. The results indicate that epinephrine and norepinephrine have an equal or more potent effect than acetylcholine in the initiation of atrial contraction after inhibition with proguanil or acetylcholine in the initiation of atrial contraction after inhibition with proguanil or acetylcholine or cessation by fatigue.

KURLAND

Preziosi, P., De Vleeschhouwer, G. R., De Schaepdryver, A. F., and Bianchi, A.: Effects of Methoxamine on the Isolated Heart and Lungs of Guinea Pig. Arch. int. pharmacodyn. **121**: 506 (Sept.), 1959.

Methoxamine, in doses ranging from 10 to 500 μg., added to the perfusing liquid of isolated guinea pig hearts induced a slight negative inotropic effect. Higher doses, up to 2 mg., exerted a very marked negative inotropic effect and also a mild chronotropic action. Sensitization of cardiac responses to acetylcholine, observed by others, did not occur. The injection of 50 to 1000 μg. of methoxamine into the pulmonary artery of isolated guinea pig lungs did not affect the bronchial tone nor did it antagonize spontaneously

occurring pneumoconstriction. Smaller doses did not counteract induced anaphylactic pneumoconstriction.

BRACHFELD

Rosenberg, S. Z., Stern, S., and Heimann-Hollaender, E.: The Role of Peripheral Venous Congestion in the Maintenance of Sustained Plasma Quinidine Level. J. Lab. & Clin. Med. 53: 849 (June), 1959.

Peripheral venous congestion, rather than congested liver or kidneys, was demonstrated to be the major factor in sustained plasma quinidine levels in 18 dogs. Experimental congestion was produced by constricting with ligatures the thoracic inferior vena cava in 4 dogs, the abdominal vena cava above the renal veins in 4 dogs, and the abdominal vena cava below the renal veins in 5 animals. Seven to 21 days later, quinidine sulfate was administered intravenously (10 mg./Kg.). Blood samples were drawn after 15, 60, 120, and 180 minutes and again 24 hours later. Plasma quinidine levels were determined by the Brodie-Udenfriend photofluorometric method. In control animals, 40.5 per cent of the quinidine was found in the plasma 3 hours after the injection, and 8 per cent, 24 hours later. In dogs with previously constricted veins, quinidine disappearance was markedly delayed. Twenty-four hours after the injection, 39 per cent was still present in the plasma of those with thoracic inferior vena caval constriction, 47 per cent in abdominal vena caval constriction above the renal veins, and 46 per cent when ligatures were below the renal veins. The same mechanism is thought to operate in human congestive heart failure.

MAXWELL

Schreiber, S. S., Oratz, M., and Rothschild, M. A.: Effect of Ouabain on Potassium Exchange in Heart Muscle Mitochondria. Am. J. Physiol. 198: 89 (Jan.), 1960.

In previous studies with the working frog ventricle it was demonstrated that intracellular potassium exchanges at 2 distinct rates with half times of approximately 10 and 60 minutes. The slower of the 2 rates varied with the amount of work performed, the external concentration of potassium, and exposure to ouabain. In the present study, the exchange of potassium in mitochondria was investigated both in a control state and after exposure to ouabain, in order to determine whether mitochondrial potassium represented the slowly exchanging compartment. Mitochondrial potassium represented only 15 per cent of the total ventricular potassium, while the slowly exchanging phase contained about 50 per cent. Ouabain perfusion was associated with inhibition of entrance of potassium into the slowly exchanging ventricular phase, but no isolated specific effect on the mitochondrial potassium was found. Alterations in mitochondrial potassium directly reflected changes within the total ventricle. The results indicate that mitochondrial potassium does not represent the major part of the slowly exchanging compartment.

KAYDEN

Winbury, M. M., and Alworth, B. L.: Suppression of Experimental Atrial Arrhythmias by Several Antihistamines. Arch. int. pharmacodyn. 122: 318 (Nov.), 1959.

The ability of a number of antihistaminic agents to suppress experimentally induced atrial arrhythmias (injury-stimulation and aconitine) was determined in anesthetized dogs. All of the compounds displayed some activity against the arrhythmias but there were differences in potency. Some compounds were highly active against 1 type of arrhythmia but not the other. Only diphenhydramine and methapyrilene had high activity against both types of arrhythmias.

BRACHFELD

Young, D. S,, Forrester, T. M., and Morgan, T. N.: A Comparison of the Diuretic Action of the Chlorothiazide Analogues. Lancet 2: 765 (Nov. 7), 1959.

An attempt is made to explain the differences in the action of chlorothiazide and 2 newer derivatives, by observing the quantity and composition of urine after their administration and the urinary excretion of the drugs after oral and intravenous therapy. Ten healthy male medical students without evidence of renal disease were investigated. After the oral administration of 2,000 mg. of chlorothiazide, 150 mg. of hydrochlorothiazide and 150 mg. of hydroflumethiazide the response appeared within 2 hours, reached a maximum in 4 hours and lasted for 12 hours in the case of the former but up to 24 hours in the latter 2. Excretion of potassium was less after the derivatives than after chlorothiazide. Similar results were observed after intravenous administration of the drugs. Chlorothiazide appeared in the urine in maximum concentration during the first half hour after intravenous administration and by 4½ hours was totally excreted. Hydrochlorothiazide, however, was detected for 8 to 10 hours. After oral administration, maximum urinary concentration was found in the first 2 to 4 hours. Thereafter, the concentration declined until, by the end of 24 hours, none could be detected. The urine concentration of all 3 diuretics ran

parallel to the diuretic effect. Compared to the other drugs, less chlorothiazide was recovered in the urine after an oral dose, suggesting incomplete absorption from the intestinal tract.

KURLAND

PHYSICAL SIGNS

Groom, D., Chapman, W., Francis, W. W., Bass, A., and Sihvonen, Y. T.: The Normal Systolic Murmur. Ann. Int. Med. 52: 134 (Jan.), 1960.

The authors recorded heart sounds from the precordium of 71 normal subjects in whom auscultation revealed no cardiac murmurs. The recordings were made on a cathode-ray oscilloscope from a high sensitivity capacitance pickup and the subjects were studied in a soundproof room. In each subject readily discernible murmurs were present extending through one fourth or more of systole, and reproducible on repeated tracings. In more than three fourths of the subjects the point of maximal intensity was between the second and fourth intercostal spaces along the left sternal border. Other features of these murmurs that are regarded as typical of functional systolic murmurs include their very low intensity, their prominent variation with changes in position and respiration, their variability from day to day and perhaps also the relative prominence of sinusoidal wave forms. The majority of the murmurs were of decrescendo configuration following the first heart sound; only about one third had a diamond-type pattern. Using the same technic the authors reported murmurs in 19 of 25 fetal hearts during the last trimester of pregnancy. In the fetus, the murmurs are presumably systolic in time and arise from shunts unique to the fetal circulation. The mechanism and site of origin of these systolic sounds in the adult are uncertain. It is suggested that they are a universal functional murmur which is usually subaudible.

KAYDEN

Silverstein, A., Doniger, D., and Bender, M. B.: Manual Compression of the Carotid Vessels, Carotid Sinus Hypersensitivity and Carotid Artery Occlusions. Ann. Int. Med. 52: 172 (Jan.), 1960.

The technic of carotid artery compression described by the authors involves the application of pressure by the fingers of one hand over the carotid artery low in the neck, and at the same time palpation of the ipsilateral temporal artery to observe loss of the superficial temporal pulse with the other hand. Compression is maintained for 30 seconds unless the patient loses consciousness or has a seizure, at which time the compression is immediately discontinued. In 26 of 40 patients with occlusive disease of the carotid arteries on 1 side, it was possible to produce syncope with seizures or seizures alone by compression of the contralateral carotid artery. In carotid sinus hypersensitivity compression of the artery low in the neck will rarely produce the hypersensitive response. The onset of syncope or seizures with carotid sinus sensitivity occurs usually within 2 or 3 seconds; ischemic effects in the brain due to compression may take several more seconds to appear. The pressure necessary to produce the hypersensitive carotid sinus response is much less than that required for cerebral vascular ischemia. The vagal and depressor types of carotid sinus sensitivity may be suspected by the appropriate pulse rate and blood pressure changes, and these can usually be excluded by repeating the test after atropine or a vasopressor drug. The authors stress that, although many patients reported to have the cerebral reflex type of carotid sinus sensitivity without changes in pulse rate or blood pressure probably have occlusive carotid artery disease, a few patients do appear to have the purely cerebral form of carotid sinus hypersensitivity.

KAYDEN

NEWS FROM THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7-9170

Gold Heart, Lasker Awards Presented by Association

Among the honors conferred by the American Heart Association at its Annual Meeting and Scientific Sessions were the following:

Gold Heart Awards

Gold Heart Awards, highest honor of the American Heart Association, were bestowed at the Association's Annual Dinner on Herrman L. Blumgart, M.D., Professor of Medicine, Harvard Medical School, Physician-in-Chief, Beth Israel Hospital, Boston, and Editor-in-Chief of *Circulation;* Robert L. King, M.D., Clinical Associate Professor of Medicine, University of Washington School of Medicine and former President of the American Heart Association; and Mr. Eddie Cantor, stage, screen and television star, who is Co-Chairman of the Association's Heart Committee of the Motion Picture Industry. They were cited for outstanding contributions in advancing the objectives of the American Heart Association.

Lasker Award

Joint recipients of the Albert D. Lasker Award of the American Heart Association for unique achievement in the field of cardiovascular research were Karl Paul Link, Ph.D., Department of Biochemistry, College of Agriculture, University of Wisconsin; Edgar V. Allen, M.D., Professor of Medicine, Mayo Foundation Graduate School, University of Minnesota, and former President of the American Heart Association; and Irving S. Wright, M.D., Professor of Clinical Medicine, Cornell University Medical College, also a past-President of the American Heart Association. The Award, which consists of a statuette of the *Winged Victory of Samothrace* and an honorarium of $2500 each, was in recognition of their leadership and outstanding achievements in the development of anticoagulant therapy.

National Research Supplemented

The Peninsula (Va.) Heart Association has contributed $5500 to the Association's national research program in support of studies being conducted by Drs. W. T. Thompson and Sami Said at the Medical College of Virginia on "Gas Exchange and the Pulmonary Capillary Circulation."

This brings to nearly $85,000 the total received from AHA affiliates and chapters for supplementary support of national research in fiscal 1960-61. Such sums support studies approved by the Association's Research Committee which could not be otherwise covered by the national research budget.

Symposium Scheduled in 1961 on Myocardial Infarction

An International Symposium on "The Etiology of Myocardial Infarction" has been scheduled to be held from November 16-18, 1961, at the Henry Ford Hospital, Detroit, Mich. (The year was erroneously listed as 1960 in the Meetings Calendar of the September issue of *Circulation*).

Further information may be obtained by writing to Thomas N. James, M.D., Chairman, Section on Cardiovascular Research, Henry Ford Hospital, Detroit 2, Mich.

Symposium on the Myocardium

A symposium on "The Myocardium—Its Biochemistry and Biophysics," under sponsorship of the New York Heart Association, will be held December 9-10, 1960, in the

Waldorf-Astoria Hotel, New York. Further information may be obtained from A. P. Fishman, M.D., Chairman of the symposium, New York Heart Association, 10 Columbus Circle, New York 19, N.Y.

Cardiology Contest Announced

A contest for the best unpublished work on a cardiological subject has been announced by Recordati Laboratorio Farmacologico, with a prize of $2000 to be presented to the winner during the Fifth World Congress on Cardiology in Mexico City in 1962. Further information regarding the contest, open to all physicians under 40, may be obtained from the firm's offices, Via Civitali 1, Milan, Italy.

Meetings Calendar

November 26-28: American College of Chest Physicians, Interim Session, Washington, D.C. Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Ill.

November 28-December 2: American Medical Association, Clinical Meeting, Washington, D.C. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Ill.

November 30-December 3: Canadian Heart Association and National Heart Foundation of Canada, Toronto. J. B. Armstrong, 501 Yonge Street, Toronto 5, Canada.

1961

January 9-12: White House Conference on Aging, Washington, D.C. Miss Esther C. Stamats, Department of Health, Education and Welfare, Washington 25, D.C.

February 8-11: American College of Radiology, Chicago. W. C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill.

March 13-16: National Health Council, New York. Philip E. Ryan. 1790 Broadway, New York 19, N.Y.

March 20-24: American Surgical Association, Boca Raton, Fla. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 10-14: American Physiological Society, Atlantic City. Ray G. Daggs, 9650 Wisconsin Ave., Washington 14, D.C.

April 17-20: American Academy of General Practice, Miami Beach. Mac F. Cahal, Volker at Brookside, Kansas City 12, Mo.

April 24-26: American Association for Thoracic Surgery, Philadelphia. Miss Ada Harvey, 7730 Carondelet Ave., St. Louis 5, Mo.

April 28-30: American Psychosomatic Society, Atlantic City. Morton F. Reiser, 265 Nassau Road, Roosevelt, N.Y.

April 30: American Federation for Clinical Research, Atlantic City. James E. Bryan, 50 W. 57th Street, New York 19, N.Y.

May 8-12: American College of Physicians, Miami Beach. E. C. Rosenow, Jr., 4200 Pine Street, Philadelphia 4, Pa.

May 16-20: American College of Cardiology, New York. Philip Reichert, 350 Fifth Avenue, New York 1, N.Y.

June 22-26: American College of Chest Physicians, New York. Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Ill.

June 26-30: American Medical Association, Annual Meeting, New York. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Ill.

November 16-18. International Symposium "Etiology of Myocardial Infarction," Detroit. Thomas N. James, Henry Ford Hospital, Detroit 2, Mich.

Abroad

1961

August 22-25: International Pharmacological Meeting (First) Stockholm. A. Wretlind, Karolinska Institutet, Stockholm 60, Sweden.

September 3-10: Inter-American Congress of Radiology, Sao Paulo. W. Bomfim-Pontes, Rau Cesario Motta, No. 112, Sao Paulo, Brazil.

September 4-7: International Congress on Rheumatology, Rome. Prof. C. B. Ballabio, Clinica Medica Generale, Via F. Sforza 35, Milano, Italy.

1962:—Fourth World Congress of Cardiology, Mexico City. I. Chavez, Ave. Cuauhtemoc, 300, Mexico, D.F.

CONTRIBUTORS TO THIS ISSUE

Crawford W. Adams, M.D.

Assistant Clinical Professor of Medicine, Vanderbilt University, School of Medicine, Nashville, Tenn.

E. Cowles Andrus, M.D.

Associate Professor of Medicine, Chief of the Cardiovascular Division, Department of Medicine, Johns Hopkins University, Baltimore, Md.; Senior Scientific Advisor to the National Heart Institute, U.S. Public Health Service.

James M. Bacos, Captain, U.S.A.F. (M.C.)

Presently on Active Duty with the United States Air Force, Assigned to Forbes Air Force Base Hospital, Kansas; Formerly, Fellow in Cardiology and Instructor in Medicine, Duke University Medical Center, Durham, N.C.

Lionel M. Bargeron, Jr., M.D.

Associate Professor Pediatric Cardiology, Department of Surgery, University of Alabama, Birmingham, Ala.

Walter Beck, M.D.

Fellow in Physiology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

Jerome B. Block, M.D.

Post Doctoral Research Fellow; U.S. Public Health Service; Present address, University of Washington, School of Medicine, Seattle, Wash.

Klaas K. Bossina, M.D.

Assistant Professor of Pediatries, University of Groningen, Netherlands.

Merrill N. Bradley, M.D.

Resident in Surgery, University of Alabama Medical Center, Birmingham, Ala.

Eugene Braunwald, M.D.

Chief, Section of Cardiology, Clinic of Surgery, National Heart Institute, Bethesda, Md.

J. David Bristow, M.D.

Raymond R. Brown Fellow in Cardiology, Oregon Heart Association, University of Oregon Medical School, Portland, Ore.

Howard B. Burchell, M.D., Ph.D., (Med.)

Consultant, Section of Medicine, Mayo Clinic; Professor of Medicine, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

Belton A. Burrows, M.D.

Associate Professor of Medicine, Boston University School of Medicine; Chief, Radioisotope Service, Boston Veterans Administration Hospital; Associate Member, Robert Dawson Evans Memorial, Associate Visiting Physician, Massachusetts Memorial Hospitals, Boston, Mass.

Leland C. Clark, Jr., Ph.D.

Associate Professor of Biochemistry, Department of Surgery, University of Alabama Medical Center, Birmingham, Ala.

John T. Eagan, M.D.

Fellow in Cardiology and Instructor in Medicine, Duke University Medical Center, Durham, N.C.

Ludwig W. Eichna, M.D.

Professor of Medicine, New York University College of Medicine; Visiting Physician, Bellevue Hospital, New York, N.Y. Present address: State University of New York, Downstate Medical Center, Brooklyn, N.Y.

Robert P. Eisinger, M.D.

Chief Resident in Medicine, Beth Israel Hospital, New York, N.Y.

Robert G. Fish, M.D.

Chief, Medical Service, Veterans Administration Hospital, Oteen, N.C.

Martin H. Floch, M.D.

Assistant Resident in Medicine, Beth Israel Hospital, New York, N.Y.

Herbert E. Griswold, M.D.

Professor of Medicine and Head, Division of Cardiology, University of Oregon Medical School, Portland, Ore.

Gerald J. Hine, Ph.D.

Senior Physicist, Boston Veterans Administration Hospital; Assistant Professor of Medicine, Boston University School of Medicine, Boston, Mass.

Orville Horwitz, M.D.

Assistant Professor of Clinical Medicine, University of Pennsylvania, Philadelphia, Pa.

Claude R. Joyner, Jr., M.D.

Assistant Professor of Medicine, University of Pennsylvania, Philadelphia, Pa.

Donald G. Kassebaum, M.D.

Howard Irwin Memorial Fellow in Cardiology, Oregon Heart Association, University of Oregon Medical School, Portland, Ore.

John W. Kirklin, M.D., M.S. (Surg.)

Consultant, Section of Surgery, Mayo Clinic; Associate Professor of Surgery, Mayo Foundation, Graduate School, University of Minnesota; Rochester, Minn.

Eugene Lepeschkin, M.D.

Professor of Experimental Medicine, University of Vermont College of Medicine; Chief Cardiographer, DeGoesbriand Memorial Hospital, Burlington, Vt.

Jerome Liebman, M.D.

Research Fellow, National Heart Institute, National Institutes of Health, U.S. Public Health Service.

Champ Lyons, M.D.

Professor and Chairman, Department of Surgery, University of Alabama Medical Center, Birmingham, Ala.

Katrina T. McArthur, M.D.

Fellow in Pediatric Cardiology, Department of Surgery, University of Alabama Medical Center, Birmingham, Ala.

Victor A. McKusick, M.D.

Professor of Medicine, Johns Hopkins University School of Medicine; Physician, Johns Hopkins Hospital, Baltimore, Md.

Clark H. Millikan, M.D.

Consultant, Section of Neurology, Mayo Clinic; Professor of Neurology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

Gerrit A. Mook, M.D.

Assistant in Physiology, University of Groningen, Netherlands.

Andrew G. Morrow, M.D.

Chief, Clinic of Surgery, National Heart Institute, Bethesda, Md.

Alexander S. Nadas, M.D.

Assistant Clinical Professor of Pediatrics, Harvard Medical School; Cardiologist, Children's Medical Center, Boston, Mass.

Edward S. Orgain, M.D.

Professor of Medicine, Director of Cardiovascular Disease Service, Duke University Medical Center, Durham, N.C.

Bernard J. Pass, M.D.

Instructor in Clinical Dermatology, Vanderbilt University, School of Medicine, Nashville, Tenn.

John Ross, Jr., M.D.

Senior Assistant Surgeon, Clinic of Surgery, National Heart Institute, Bethesda, Md.

Stewart M. Scott, M.D.

Assistant Chief, Cardiovascular Surgery, Veterans Administration Hospital, Oteen, N.C.

Robert G. Siekert, M.D., M.S. (Anat.)

Consultant, Section of Neurology, Mayo Clinic; Assistant Professor of Neurology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

Mark M. Singer, M.D.

Assistant Resident in Medicine, Beth Israel Hospital, New York, N.Y.

Albert Starr, M.D.

Assistant Professor of Surgery, Division of Thoracic Surgery, University of Oregon Medical School, Portland, Ore.

H. J. C. Swan, M.B., M.R.C.P., Ph.D.

Consultant, Section of Physiology, Mayo Clinic; Assistant Professor of Physiology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

Timothy Takaro, M.D., M.S. (Surg.)

Chief, Cardiovascular Surgery, Veterans Administration Hospital, Oteen, N.C.

Jack P. Whisnant, M.D., M.S (Neurol.)

Consultant, Section of Neurology, Mayo Clinic; Instructor in Neurology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

Phyllis G. Williams, B.S.

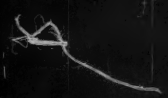
Research Assistant, Robinette Foundation, Hospital of the University of Pennsylvania, Philadelphia, Pa.

Willem G. Zijlstra, M.D.

Assistant Professor of Physiology, University of Groningen, Netherlands.

Gary Zucker, M.D.

Associate Physician, Beth Israel Hospital, New York, N.Y.



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